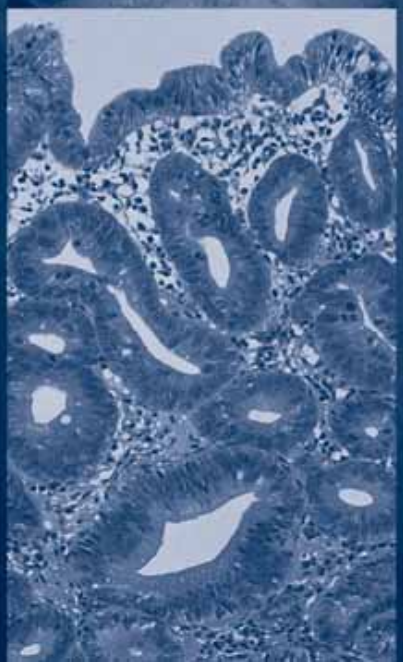
R. Fujita • J.R. Jass • M. Kaminishi
R.J. Schlemper (Eds.)

Early Cancer of the Gastrointestinal Tract

Endoscopy, Pathology, and Treatment



Springer

R. Fujita, J.R. Jass, M. Kaminishi, R.J. Schlemper (Eds.)
Early Cancer of the Gastrointestinal Tract
Endoscopy, Pathology, and Treatment

R. Fujita, J.R. Jass
M. Kaminishi, R.J. Schlemper (Eds.)

Early Cancer of the Gastrointestinal Tract

Endoscopy, Pathology, and Treatment

With 353 Figures, Including 289 in Color

Springer

Rikiya Fujita, M.D.
Chief of Endoscopy Division, Gastroenterology Center, Cancer Institute Hospital
3-10-6 Ariake, Koto-ku, Tokyo 135-8550, Japan

Jeremy R. Jass, M.D.
Department of Pathology, McGill University
Duff Medical Building, 3775 University Street, Montreal, Quebec, Canada H3A 2B4

Michio Kaminishi, M.D., Ph.D.
Department of Gastrointestinal Surgery, The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Ronald J. Schlemper, M.D., Ph.D.
Specialist in Internal Medicine and
Medical Director, International Clinic Tojinmachi
1-4-6 Jigyo, Chuo-ku, Fukuoka 810-0064, Japan

Library of Congress Control Number: 2005935946

ISBN10 4-431-22872-1 Springer-Verlag Tokyo Berlin Heidelberg New York
ISBN13 978-4-431-22872-1 Springer-Verlag Tokyo Berlin Heidelberg New York

Springer is a part of Springer Science+Business Media
springeronline.com

Printed in Japan

Typesetting: SNP Best-set Typesetter Ltd., Hong Kong
Printing and binding: Shinano, Inc., Japan

Printed on acid-free paper

Foreword

First of all, I would like to discuss two undeniable facts. One is that cancers that are malignant neoplasias of the gastrointestinal tract are epithelial in origin, so it is natural that they grow from the mucosa of the gastrointestinal tract. Another is that an early stage of the cancer invariably exists in the mucosa. Because an early diagnosis is extremely important in the initial stages of cancer in the gastrointestinal tract, the following studies in this book are indispensable to reveal the growth and extension of the disease.

For a long time there has been a decisive difference between Japanese and Western pathologists in the understanding of early cancer. That is, Japanese pathologists diagnose intramucosal neoplastic lesions that have remarkable cellular atypia and structural atypia as cancers, but most Western pathologists don't accept that and diagnose them as dysplasias. They diagnose as cancers only those lesions that show invasion. In a sense, these diagnoses are based on philosophical and conceptual differences in thinking. One Western gastroenterologist described Japanese diagnostic methodology as "Japanese fairy tales." Prof. Manfred Stolte analyzes this point of view in this book and notes that it might better be described as a "Western deficiency."

If we leave this problem untouched, however, studies of gastrointestinal cancers may be deadlocked. How to fill the gap between Japanese and Western interpretations? Is it possible to obtain a unified view or a consensus on pathological findings of cancers? I believe that if Japanese and Western pathologists were to examine full sets of biopsy and resection specimens simultaneously, including endoscopic findings, and through discussion make a mutual diagnosis, the gap might be filled. I believed that resolution of this problem was absolutely necessary, so I adopted it as the main theme when I took up my presidency of the general meeting of the Japanese Society of Gastrointestinal Endoscopy. This book is a compilation of major aspects of that meeting.

Actually, these attempts had already been made in the TNM classification and the Vienna consensus criteria for pathological diagnosis, which are mentioned in this book, but they are still incomplete in spite of remarkable progress. We hope that the information from this book may lead to a more general understanding, and may help to settle existing differences.

Dr. Ronald J. Schlemper collected biopsy and resection specimens, including specimens from 12 gastric cases, 7 colorectal cases and 5 esophageal cases, which are described at the beginning of this book. His work is admirable. By comparing these corresponding specimens readers may ascertain that resection specimens (most of them are endoscopic mucosectomy specimens of the stomach) appear to be more malignant than biopsy specimens. This may be an important key to finding intramucosal cancers. Furthermore, readers may well recognize that certain differences exist between Japanese and Western pathologists' diagnoses. The classification used to detect the existence of intramucosal signet ring cell carcinoma or poorly differentiated adenocarcinoma may be a major breakthrough. When many cases like these are collected, if Japanese and Western pathologists examine the same specimens and discuss them without prejudice, an advanced consensus may be produced and the study of gastrointestinal cancers may be improved. I am sincerely looking forward to that.

Takeshi Oohara, M.D., Ph.D.
President Emeritus, Tsuru-City Hospital
President Emeritus, Japanese Society of
Gastroenterological Carcinogenesis

Foreword

This is a thoroughly unusual book—not so much because of its title, but because 31 leading pathologists from 12 countries have compared their experiences in treating patients. They subjected the results from biopsies and resections of 24 patients with early neoplastic changes of the gastrointestinal hollow organ to a blind study and comparison. The results of this study had provided the basis of the Vienna Classification of Gastrointestinal Epithelial Neoplasia, published on the occasion of the 1998 World Congress of Gastroenterology in Vienna. It was demonstrated then that Western and Japanese pathologists had, as expected, formed different opinions based on their assessments of identical changes in the mucous membrane. Where, for example, the histological assessments of Western pathologists of case 1 (early cancer of the stomach) covered a wide range, from an adenoma with a low-level dysplasia ($n = 1$) to an intramucosal carcinoma ($n = 7$), all of their Japanese colleagues had diagnosed a carcinoma. These differences are due to the fact that many Western pathologists classify changes of the mucous tissue without any definite indication of invasion as a dysplasia, whereas the same findings will be diagnosed by Japanese doctors as well-differentiated adenocarcinomas, as long as they share their cellular and structural atypias. This problem is particularly acute for biopsy preparations from the surface of mucous tissue changes without obvious indications of infiltration into deeper-lying areas of the mucous tissue.

We cannot thank the editors enough for having compiled this complex work. The book is particularly important because it goes beyond the mere description of the problems created by differing histological diagnoses of "early" neoplasias of the digestive tract; it also interprets and explains them.

This section of the book is accompanied and further enriched by excellent descriptions of clinical images and such endoscopic diagnostic techniques as chromoendoscopy and endosonography (including their pitfalls), as well as magnificent images of the superior quality that we have come to expect from our Japanese colleagues over the years.

The term "early" tumors is, of course, not quite up-to-date, because its qualitative assessment of the time factor seems to defy any integration into the more common tumor classifications. Early stomach carcinomas, which by definition include carcinomas of the mucous tissue and the submucosa, are nowadays classified as T1(M) or T1(SM). This differentiation is important because these carcinomas require different therapies. In *The Gastric Cancer Treatment Guideline* from 2004, for instance, the Japanese Gastric Cancer Association recommended performing an endoscopic mucosal resection (EMR) for T1(M) tumors and differentiated gastrectomy variations for T1(SM) tumors. Some endoscopists, meanwhile, are performing an endoscopic submucosal dissection (ESD) for the latter. Nevertheless, these guidelines of the Japanese Gastric Cancer Association remain interesting and obligatory reading for every gastroenterologist and abdominal surgeon with an interest in digestive oncology.

Please allow me to conclude my remarks by reminding readers of the unique achievements of Rudolf Konjetzny, surgeon at the Eppendorf University Clinic in Hamburg in the early years of the previous century. By 1913 he had pointed out a connection between gastritis and stomach cancer. Later he discovered changes in the gastric mucous membrane, which he interpreted as the first stage of cancer and which he initially described as a "pre-carcinomatous state." In the face of the typical contemporary pathological definition of stomach carcinoma as "deep-reaching, destructive growth," Konjetzny emphasized the striking similarity of the mucosal syndrome with an "indubitable carcinoma which is spreading into the deeper-lying layers of the abdominal wall." In 1940, he finally described a stomach cancer "whose growth is restricted to the mucous membrane." It was also Konjetzny who provided evidence for the hypothesis that stomach carcinomas are preceded by a chronic gastritis with metaplasia and "unusual glandular growth in different shapes which originates from the upper epithelium, by multilayered dark epitheloid coronae without basal membrane and by many cell divisions." Today we know that the *Helicobacter pylori* bacterium is the culprit for acute and chronic gastritis, which may in turn cause peptic ulcers or metaplasia, dysplasia, and finally the development of carcinoma.

I hope that this book will find the wide readership it doubtlessly deserves. It will prove to be an indispensable guide and companion not only for pathologists, but also for gastroenterologists and surgeons.

Dr. med. Meinhard Classen, Dr. hc mult.
Emeritus Professor of Medicine, Second Department of Medicine, Technische Universität München, Germany

Foreword

Worldwide, in the year 2005 there were approximately 10 million new cases of cancer and 6.2 million deaths from cancer, according to the most recent data available from the World Health Organization. Digestive cancers account for the highest incidence and mortality of cancer worldwide, with 3 million new cases and 2.2 million deaths annually (colorectal, esophageal and stomach, liver and pancreas). Because of the increasing size and aging of populations in both developed and developing countries, the absolute number of many of these cancers will dramatically increase over the next few years. National health policy in every country should be concerned with the prevention of digestive cancers. The gastroenterologist, primary care physician, endoscopist, surgeon, oncologist, and other health-care providers have a major role in the prevention of digestive cancers. A critical role is in endoscopic detection of early cases and premalignant disease (e.g., Barrett's and adenomas) in asymptomatic persons. Primary prevention is also of critical importance, especially in certain cancers, such as gastric cancer where *Helicobacter pylori* infection has been shown to be responsible for approximately 50% of these cancers, in addition to such dietary factors as diets poor in fruits and vegetables and rich in salt. Genetic susceptibility also plays a role, and the effect of chemoprevention in some digestive cancers is under rigorous study.

There are worldwide differences in the detection and management of early gastrointestinal cancers, especially when one compares the Japanese and Western experiences. This book addresses those differences superbly. Its format is novel, exciting, and very informative. Cases are presented, endoscopy described, and then Western and Japanese pathologists interpret biopsy specimens. Their interpretation was compared to the pathology of resected specimens. Commentary is then made on both the endoscopic and pathologic interpretation, with a view toward arriving at an understanding of the differences. This is unique. The approach provides insight into the two contrasting viewpoints. The second part of the book enhances this format with more didactic presentations of various aspects of diagnosis and management of gastrointestinal cancers in general and also specific cancers, such as gastric and colorectal cancers. These topics include a discussion of the Vienna classification for pathological diagnosis, early cancer in Barrett's esophagus, endoscopic ultrasound, endoscopic treatment, and survival rates of early cancer. All of the cases and topics deal with the luminal gastrointestinal cancers, i.e., of the esophagus, stomach, and colorectum. The book is an ambitious undertaking in terms of its unusual clinical–endoscopic–pathological integrative format and its presentation and discussion of Japanese and Western viewpoints. It has succeeded in bringing together contrasting perspectives by some of the world's most experienced, skilled, and knowledgeable endoscopists, pathologists, and clinicians. The book is truly a remarkable learning experience and achievement. It should be read and studied by everyone involved in the detection and management of patients at risk of digestive cancers.

Sidney J. Winawer, M.D., MACG, Dr. of Sci (Hon)
Professor of Medicine, Weill Medical College
of Cornell University
Paul Sherlock Chair, Memorial
Sloan-Kettering Cancer Center
Co-Chairman, International Digestive Cancer Alliance

Foreword

It is a great pleasure to see the publication of *Early Cancer of the Gastrointestinal Tract,* compiled by Professor Fujita, Professor Jass, Professor Kaminishi, and Dr. Schlemper.

Because early cancer in the gastrointestinal tract—above all, early gastric cancer—is very common in Japan, its diagnosis is not generally considered to be very complicated, except in special cases. However, the concept of what we call early gastric cancer in Japan was not easily understood in Europe and the United States at first. The reason was that the number of early gastric cancer cases itself was very small in Europe and the United States, and if diagnosed at all, they were classified as dysplasia, not cancer.

Recently, it has gradually become known that there are early gastric cancer cases in Europe and United States as well, and the classification of early gastric cancer established by the Japan Gastroenterological Endoscopy Society has been widely acknowledged. Still, there exists a wide gap in awareness.

That gap between Japan on the one hand and Europe and the United States on the other regarding gastrointestinal tract cancer was revealed in two papers written by Dr. Ronald J. Schlemper (who also wrote a chapter in this book) and his colleagues. One was "Diagnostic criteria for gastrointestinal carcinoma in Japan and Western countries: proposal for a new classification system of gastrointestinal epithelial neoplasia," published in the *Journal of Gastroenterology and Hepatology* in 2000, and the other was "Vienna classification of gastrointestinal epithelial neoplasia," published in *Gut* the same year.

The Vienna classification of gastrointestinal epithelial neoplasia was completed by asking 31 well-known pathologists in 12 countries to examine 76 pathological specimens of mostly early neoplastic lesions, and then compiling the members' opinions in a meeting held in Vienna in September 1998.

In Chapter One of this book, many cases offered for this pathological study are presented with the views of endoscopy commentators and pathology commentators, which include many famous endoscopists and pathologists from Japan and other countries. The composition of the cases comprised 12 gastric cases, 7 colorectal cases, and 5 esophageal cases.

The correlation between the biopsied specimens and endoscopically or surgically resected specimens was intentionally concealed from the 31 pathologists in order to reveal the difference of the views among them. By examining the Tables that show those differing views, readers can see how different pathological interpretation can be from person to person, culture to culture. It seems we have a long way to go before achieving a consensus of opinions among specialists in Japan, Europe, and the United States.

In Chapter Two, the details of the Vienna consensus criteria for pathological diagnosis are presented. Although the definitions of dysplasia, neoplasia, and carcinoma in situ are agreed upon, it is stated that Japanese pathologists are more likely to make diagnoses of cancer, while European and American counterparts do not diagnose the same cases as cancer but as dysplasia. Again, we find there is still a wide gap between different cultures.

Featured in the following chapters are early cancer in Barrett's esophagus, how to detect an early cancer, the effectiveness of EUS, endoscopic treatment for early cancer in the gastrointestinal tract, the natural course of an early cancer, surgical treatment, and survival rate of early cancer. The sections on early cancer in the gastrointestinal tract are summarized concisely.

This is the first book to compile in a straightforward manner the views of leading endoscopists and pathologists in Japan, Europe, and the United States on the same early cancer cases in the gastrointestinal tract. It graphically depicts the differences of opinions between different cultures.

Efforts to exchange views will be increasingly important in the future to bridge the gap in pathological diagnosis of early cancers in the gastrointestinal tract. To know the differing views of different specialists about the same cases has significant value. This book will play a critical role in promoting global consensus on early cancer cases in the gastrointestinal tract. It is a book that every endoscopist and pathologist should read to exchange opinions on a global basis.

Hirohumi Niwa, M.D.
President, World Organization for Digestive Endoscopy
President, Japan Gastroenterological Endoscopy Society
Professor of Medicine, St. Marianna University School of Medicine

Preface

Advanced cancers of the gastrointestinal tract develop from either superficial neoplasm or early cancer, and if they could be identified in these stages by endoscopy and diagnosed pathologically as cancer by biopsy, the benefit for patients would be immeasurable. We hope that the global dissemination of this knowledge and the techniques for the diagnosis and therapy of either superficial neoplasm or early cancer will be of worldwide benefit.

Differences in the diagnostic criteria for cancer of the gastrointestinal tract, especially for early cancer, between Japanese and Western pathologists have been a long-standing issue. Surgically resected specimens of either superficial esophageal cancer, early gastric cancer, or early colon cancer have often been diagnosed as dysplasia by Western pathologists. Gastroenterologists, endoscopists, and gastrointestinal surgeons have been unable to resolve this issue. This became a topic of personal interest during a lecture and live demonstration in a Western country. In the autumn of 1996, eight pathologists from Japan, North America, and Europe gathered and reviewed the same pathological specimens during the Asian Pacific Congress in Yokohama, Japan. R.J. Schlemper, who was a visiting scientist at Showa University Fujigaoka Hospital at that time, worked as the coordinator and raised this issue. In 1997, T. Oohara, president of the 53rd Congress of the Japan Gastroenterological Endoscopy Society, chose it as a topic of the congress, addressing it in an international symposium. Publication of Dr. Schlemper's article in *Lancet* (1997;349:1725–9) eventually led to the Vienna classification. More recently, it was our great honor and pleasure for the Japanese macroscopic classification to be recognized internationally as the Paris classification (2003). In this way, M. Kaminishi, who succeeded Professor Oohara, J.R. Jass, who attended the international symposium, R.J. Schlemper, and R. Fujita were appointed as the planning editors of this book.

The main feature of this book is that it is organized in the form of contrasting the views of East and West, bringing in the opinions of world experts in both endoscopic and microscopic specialities. From Japan, where early cancer has been intensively studied, we believe we have collected important articles exploring the natural history of early cancer, which has been demonstrated to develop into advanced cancer. We have also included an article describing many cases of Barrett's cancer, though rare in Japan, from Professor Stolte. The diagnostic methods for early cancer, including chromoscopy, magnifying endoscopy, and narrow band imaging (NBI) are still developing. Even endoscopic therapies, such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), as well as laparoscopic surgery and combination therapies, are in their developmental stages. Since more than five years have passed from the planning of this book to its publication, we asked the authors for additions and revisions immediately before publication. We would like to sincerely thank them for their cooperation.

The 12 gastric and 5 esophageal cases presented in Part 1 are from Showa University Fujigaoka Hospital, 5 of the 7 colorectal cases (13–17) are from National Cancer Center Hospital, Tokyo, and 2 colorectal cases (18 and 19) are from Niigata University School of Medicine. We would like to thank these patients and their physicians for their contribution to the clinical, endoscopic and pathological material presented. In particular we would like to thank Professor H. Watanabe, who made almost all photographs of the histological material in his office in Niigata University in 1996, and Dr. T. Shimoda, who helped to collect clinical data for the National Cancer Center Hospital cases in September 2005.

We would also like to especially acknowledge the invaluable assistance of the editorial staff at Springer-Verlag Tokyo, for their devoted efforts in the preparation and editing of this book.

September 2005
Editors
R. Fujita
J.R. Jass
M. Kaminishi
R.J. Schlemper

Contents

List of Authors

Aoki, Fumio (Chap. VII-1)
Department of Gastrointestinal Surgery, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Axon, Anthony T.R. (Chap. I-2)
Department of Gastroenterology, Room 190A Clarendon Wing, The General Infirmary at Leeds, Great George Street, Leeds LS1 3EX, UK
e-mail: anthony.axon@leedsth.nhs.uk

Chiba, Tsutomu (Chap. VI-3)
Division of Gastroenterology and Hepatology, Department of Internal Medicine, Graduate School of Medicine, Kyoto University, 54 Kawara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan

Crespi, Massimo (Chap. I-4)
National Cancer Institute, Viale Regina Elena 291, Rome 00161, Italy
e-mail: mcrespi@uni.net

Dawsey, Sanford M. (Chap. I-4)
Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard, Suite 320, Rockville, MD 20852, USA
e-mail: dawseys@mail.nih.gov

Dohmoto, Matatoshi (Chap. IV-4)
Tokushukai General Hospital Yamagata, 2-89-6 Kiyosumi-cho, Yamagata 990-0834, Japan
e-mail: md2002@nifty.com

Dostler, Irina (Chap. III-1)
Institute of Pathology, Klinikum Bayreuth, Preuschwitzer Str. 101, 95445 Bayreuth, Germany

Ell, Christian (Chap. III-1)
Dr. Horst-Schmidt-Klinikum, 65199 Wiesbaden, Germany

Fujii, Shigehiko (Chap. VI-3)
Department of Surgical and Molecular Pathology, Dokkyo University School of Medicine, 880 Kitakobayashi, Mibu, Shimotsuga, Tochigi 321-0293, Japan
e-mail: s-fujii@dokkyomed.ac.jp

Fujimori, Takahiro (Chap. VI-3)
Department of Surgical and Molecular Pathology, Dokkyo University School of Medicine, 880 Kitakobayashi, Mibu, Shimotsuga, Tochigi 321-0293, Japan

Fujisaki, Junko (Chap. IV-1)
Endoscopy Division, Gastroenterology Center, Cancer Institute Hospital, 3-10-6 Ariake, Koto-ku, Tokyo 135-8550, Japan

Fujita, Rikiya (Chap. IV-1)
Chief of Endoscopy Division, Gastroenterology Center, Cancer Institute Hospital, 3-10-6 Ariake, Koto-ku, Tokyo 135-8550, Japan
e-mail: rikiya.fujita@jfcr.or.jp

Gossner, Liebwin (Chap. III-1)
Dr. Horst-Schmidt-Klinikum, 65199 Wiesbaden, Germany

Hayashi, Kazuhiko (Chap. IV-3)
Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

Hiki, Naoki (Chap. VII-1)
Surgery Division, Gastroenterology Center, Cancer Institute Hospital, 3-10-6 Ariake, Koto-ku, Tokyo 135-8550, Japan

Hoshino, Yoko (Chap. IV-3)
Gastrointestinal Endoscopy Institute of Gastroenterology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

Itabashi, Masayuki (Chap. I-4)
Department of Pathology, Ibaraki Prefectural Central Hospital and Cancer Center, 6528 Koibuchi, Tomobe-machi, Nishiibaraki-gun, Ibaraki 309-1703, Japan
e-mail: m-itabashi@chubyoin.pref.ibaraki.jp

Iwashita, Akinori (Chap. I-3)
Department of Pathology, Fukuoka University Chikushi Hospital, 377-1 Zokumyoin, Chikushino, Fukuoka 818-8502, Japan
e-mail: iwa-aki@fukuoka-u.ac.jp

Jass, Jeremy R. (Chaps. I-3, II-1)
Department of Pathology, McGill University, Duff Medical Building, 3775 University Street, Montreal, Quebec, Canada H3A 2B4
e-mail: jeremy.jass@mcgill.ca

Kaminishi, Michio (Chaps. V-2, VII-1)
Department of Gastrointestinal Surgery, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: e05011@h.u-tokyo.ac.jp

Kashida, Hiroshi (Chap. VI-4)
Digestive Disease Center, Showa University, Northern Yokohama Hospital, 35-1 Chigasaki-chuo, Tsuzuki-ku, Yokohama 224-8503, Japan
e-mail: kashi-md@xf6.so-net.ne.jp

Kato, Yo (Chap. I-2)
Department of Pathology, Cancer Institute, 3-10-6 Ariake, Koto-ku, Tokyo 135-8550, Japan
e-mail: kato@jfcr.or.jp

Kawahara, Masaki (Chaps. I-3, V-2, VII-1)
Division of Surgery, Kanto Central Hospital, 6-25-1 Kamiyoga, Setagaya-ku, Tokyo 158-8531, Japan
e-mail: mkawahara-ths@umin.ac.jp

Kitajima, Kazuaki (Chap. VI-3)
The Third Department of Internal Medicine Oita University Faculty of Medicine, 1-1 Hasama-machi, Oita 879-5593, Japan
e-mail: KAZZ@med.oita-u.ac.jp

Kudo, Shin-ei (Chap. VI-4)
Digestive Disease Center, Showa University, Northern Yokohama Hospital, 35-1 Chigasaki-chuo, Tsuzuki-ku, Yokohama 224-8503, Japan
e-mail: kudos@med.showa-u.ac.jp

Lambert, René (Chap. V-4)
International Agency for Research on Cancer, 150, cours Albert-Thomas, F-69372, Lyon cedex 08, France
e-mail: lambert@iarc.fr

Mafune, Ken-ichi (Chap. VII-1)
Department of Gastrointestinal Surgery, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Makuuchi, Hiroyasu (Chap. V-5)
Department of Surgery, Tokai University School of Medicine, Boseidai, Isehara, Kanagawa 259-1193, Japan

Matsui, Toshiyuki (Chap. VI-1)
Department of Gastroenterology, Fukuoka University, Chikushi Hospital, 377-1 Zokumyoin Ooaza, Chikushino, Fukuoka 818-8502, Japan

May, Andrea (Chap. III-1)
Dr. Horst-Schmidt-Klinikum, 65199 Wiesbaden, Germany

Mimura, Toshiki (Chap. VII-1)
Department of Gastrointestinal Surgery, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Mitsunaga, Atsushi (Chap. IV-3)
Gastrointestinal Endoscopy Institute of Gastroenterology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

Murata, Yoko (Chap. IV-3)
Murata Clinic, Murata Bldg. 1F, 2-16-5 Nishi-Shimbashi, Minato-ku, Tokyo 105-0003, Japan
e-mail: m-yoko@terra.dti.ne.jp; murata@gi-clinic.jp

Muto, Tetsuichiro (Chap. VI-2)
Director, Cancer Institute Hospital, 3-10-6 Ariake, Koto-ku, Tokyo 135-8550, Japan
e-mail: muto@jfcr.or.jp

Nakamura, Shinichi (Chap. IV-3)
Gastrointestinal Endoscopy Institute of Gastroenterology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

Nomura, Sachiyo (Chap. VII-1)
Department of Gastrointestinal Surgery, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Ohta, Masahiko (Chap. IV-3)
Surgery, Institute of Gastroenterology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

Ohtsuka, Kazuo (Chap. VI-4)
Digestive Disease Center, Showa University, Northern Yokohama Hospital, 35-1 Chigasaki-chuo, Tsuzuki-ku, Yokohama 224-8503, Japan

Sakai, Yoshihiro (Chap. V-3)
Chief of Division of Digestive Endoscopy, Department of Medicine, Toho University, Ohashi Hospital Tokyo, 2-17-6 Ohashi, Meguro-ku, Tokyo 153-8515, Japan
e-mail: y-sakai@oha.toho-u.ac.jp

Schlemper, Ronald J. (Chaps. I-1, I-2, I-3, I-4)
Medical Director, International Clinic Tojinmachi (Internal Medicine and Gastroenterology), 1-4-6 Jigyo, Chuo-ku, Fukuoka 810-0064, Japan
e-mail: schlemper@internationalclinic.org

Seto, Yasuyuki (Chap. VII-1)
Surgery Division, Gastroenterology Center, Cancer Institute Hospital, 3-10-6 Ariake, Koto-ku, Tokyo 135-8550, Japan

Shimizu, Nobuyuki (Chap. VII-1)
Department of Gastrointestinal Surgery, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Shimizu, Seiji (Chap. IV-2)
Department of Gastroenterology, JR West General Hospital, 1-2-22 Matsuzaki-cho, Abeno-ku, Osaka 545-0053, Japan
e-mail: shimizus@oregano.ocn.ne.jp

Shimoyama, Shoji (Chap. VII-1)
Department of Gastrointestinal Surgery, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Stolte, Manfred (Chaps. I-2, I-5, III-1)
Institute of Pathology, Klinikum Bayreuth, Preuschwitzer Strasse 101, D-95445 Bayreuth, Germany
e-mail: Pathologie.Klinikum-Bayreuth@t-online.de

Tada, Masahiro (Chap. IV-2)
Tada Gastroenterological Clinic, 24 Umetada-cho, Nakagyo-ku, Kyoto 604-8136, Japan

Takahashi, Hiroshi (Chaps. IV-1, V-1)
Cancer Screening Center, Cancer Institute Hospital, 3-10-6 Ariake, Koto-ku, Tokyo 135-8550, Japan
e-mail: hiroshi.takahashi@jfcr.or.jp

Takayama, Yukiko (Chap. IV-3)
Gastrointestinal Endoscopy Institute of Gastroenterology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

Takeshita, Kimiya (Chap. I-4)
Department of Endoscopic Diagnostics and Therapeutics, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan
e-mail: take.srg1@tmd.ac.jp

Takeuchi, Tsukasa (Chap. VI-4)
Digestive Disease Center, Showa University, Northern Yokohama Hospital, 35-1 Chigasaki-chuo, Tsuzuki-ku, Yokohama 224-8503, Japan

Terano, Akira (Chap. VI-3)
President, Dokkyo University School of Medicine, 880 Kitakobayashi, Mibu, Shimotsuga, Tochigi 321-0293, Japan

Vieth, Michael (Chap. III-1)
Institute of Pathology, Klinikum Bayreuth, Preuschwitzer Strasse 101, D-95445 Bayreuth, Germany

Williams, Christopher B. (Chap. I-3)
St. Mark's Hospital, Watford Rd., Harrow, Middlesex, HA1 3UJ, England, UK
e-mail: christopherbwilliams@btinternet.com

Yamaguchi, Hirokazu (Chap. VII-1)
Department of Gastrointestinal Surgery, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Yasuda, Kenjiro (Chap. IV-5)
Department of Gastroenterology, Kyoto Second Red Cross Hospital, 355-5 Haruobi-cho, Marutamachi-agaru, Kamigyo-ku, Kyoto 602-8026, Japan
e-mail: yasuda-k@tim.hi-ho.ne.jp

Yoshida, Misao (Chap. VI-5)
Surgery, Metropolitan Bokutoh Hospital, 4-23-15 Kotobashi, Sumida-ku, Tokyo 130-8575, Japan
e-mail: misao-yoshida@bokutoh-hp.metro.tokyo.jp

Yoshida, Shigeaki (Chap. I-2)
National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan
e-mail: syoshida@east.ncc.go.jp

Yoshino, Junji (Chap. VI-1)
Department of Internal Medicine, Second Teaching Hospital, Fujita Health University, School of Medicine, 3-6-10 Otobashi, Nakagawa-ku, Nagoya 454-8509, Japan
e-mail: jyoshino@fujita-hu.ac.jp

I. Case Presentations: Clinical Data, Endoscopy, and Pathology

Contents of Part I

1. Introduction

Ronald J. Schlemper

The following 12 gastric, 7 colorectal, and 5 esophageal cases are part of the material used in previous studies [1–4]. In total, 76 histological specimens of mostly early neoplastic lesions were circulated to and individually reviewed by 31 well-known pathologists from 12 countries a few months before the "Vienna meeting," which was held on 5 and 6 September, 1998, and led to the Vienna classification of gastrointestinal epithelial neoplasia [1]. In Tables 1–24, the results of the assessments by these 31 pathologists are shown for 41 of the 76 specimens. These 41 specimens were taken from lesions in 23 Japanese patients, of which the endoscopic gross appearances are indicated by I, IIa, IIb, IIc, IIa+IIc or IIc+IIa according to the macroscopic classification of early neoplasia of the digestive tract [5].

The histological material reviewed by the 31 pathologists consisted of resection specimens, the assessments of which are indicated in the tables by circles, and biopsy specimens from the same lesions, indicated by crosses. The pathologists were not told the relationship of biopsy and resection specimens. They were asked to make a diagnosis of each histological specimen by choosing from the following items: negative for neoplasia (normal, reactive, or regenerative epithelium), indefinite for neoplasia, low-grade adenoma/dysplasia, high-grade adenoma/dysplasia, suspicious of carcinoma, and definite carcinoma, subclassified by the depth of invasion: (a) no invasion (Japanese viewpoint), (b) intramucosal invasion (into the lamina propria or muscularis mucosae), and (c) submucosal invasion [2].

In Tables 1–24, the nine Japanese specialists in gastrointestinal pathology are indicated by the red capitals "J." For each organ system, Western pathologists who diagnosed suspected or definite carcinoma in a similar percentage of cases as these Japanese specialists were considered (and most considered themselves) to have a Japanese viewpoint and are indicated by the red capitals "W;" these included pathologists from Germany, Austria, the United Kingdom, and Korea. The remaining pathologists diagnosed carcinoma in a lower percentage of cases than the Japanese specialists; these pathologists with a Western viewpoint are indicated by the blue capitals "W" and were from Finland, Sweden, Belgium, France, Germany, Austria, Italy, the United Kingdom, Korea, Canada, and the United States. There were two general pathologists from Japan who diagnosed in a manner similar to most Western pathologists and are indicated by the blue capitals "J."

The differences in diagnoses between most Western and Japanese pathologists were considerable. Suspected or definite carcinoma was diagnosed in 17%–66% of gastric, in 5%–40% of colorectal, and in 10%–67% of esophageal specimens by pathologists with a Western viewpoint, but in 77%–94% of gastric, in 45%–75% of colorectal, and in 81%–100% of esophageal specimens by pathologists with a Japanese viewpoint [1, 2]. Tables 1–24 depict the individual diagnoses of all 31 pathologists. For example, from Table 1 one can see that ten Western pathologists diagnosed both the biopsy and the resection specimen of this lesion as high-grade adenoma/dysplasia and three diagnosed the biopsy similarly but the resection specimen as suspected or intramucosal carcinoma, whereas of the nine Japanese specialists six diagnosed both specimens as noninvasive carcinoma, two diagnosed the biopsy as noninvasive but the resection specimen as intramucosal carcinoma, and one diagnosed both as intramucosal carcinoma.

Such diagnostic differences and discrepancies between biopsy-based and resection-based diagnoses can, in large part, be resolved by adopting the revised Vienna classification [2–4, 6]. In this classification, high-grade adenoma/dysplasia, suspected, noninvasive and intramucosal carcinoma are grouped together into one clinically relevant category termed "mucosal high-grade neoplasia." Endoscopic or surgical local resection is indicated for all lesions falling into this category. This is well illustrated by the following 24 cases.

References

1. Schlemper RJ, Riddell RH, Kato Y, et al (2000) The Vienna classification of gastrointestinal epithelial neoplasia. Gut 47:251–255
2. Schlemper RJ, Kato Y, Stolte M (2000) Diagnostic criteria for gastrointestinal carcinomas in Japan and Western countries: proposal for a new classification system of gastrointestinal epithelial neoplasia. J Gastroenterol Hepatol 15:G49–G57
3. Schlemper RJ, Kato Y, Stolte M (2001) Review of histological classifications of gastrointestinal epithelial neoplasia: differences in diagnosis of early carcinomas between Japanese and Western pathologists. J Gastroenterol 36:445–456
4. Schlemper RJ, Iwashita A (2004) Classification of gastrointestinal epithelial neoplasia. Current Diagn Pathol 10:128–139
5. Schlemper RJ, Hirata I, Dixon MF (2002) The macroscopic classification of early neoplasia of the digestive tract. Endoscopy 34:163–168
6. Dixon MF (2002) Gastrointestinal epithelial neoplasia: Vienna revisited. Gut 51:130–131

2. Early Cancer of the Stomach (Cases 1–12)

Case 1, IIc

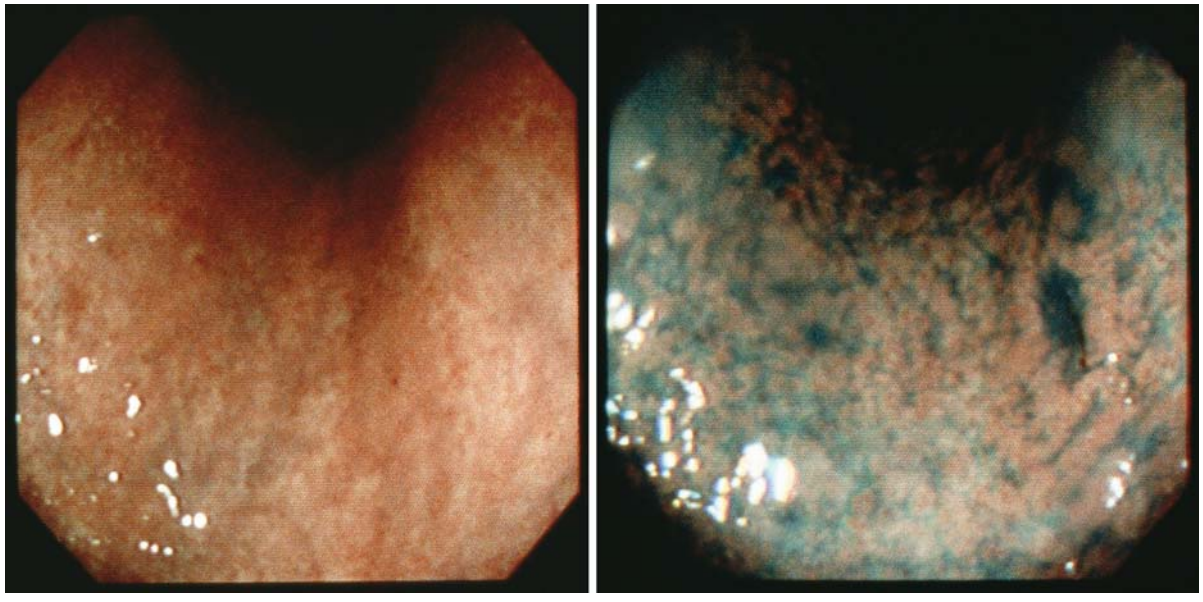


Fig. 1. **A** Corpus, lesser curvature (U-turn view). **B** Same site after spraying indigo carmine

Case Description

A man, aged 73 years, complaining of anorexia, cough, and rhinorrhea for a week, underwent a barium meal examination, which was followed up by an upper gastrointestinal (GI) endoscopic examination to rule out abnormalities. A lesion of about 5 mm in diameter was found in the corpus and was biopsied. Two months later he underwent endoscopic ultrasonographic examination and shortly thereafter endoscopic resection was performed. The resection margins were free of tumor. On follow-up endoscopic examinations, no local recurrence was found.

Endoscopy Commentary

ANTHONY T.R. AXON (UK)[1]

History

A 73-year-old man complaining of anorexia, cough, and rhinorrhea for a week would not in the United Kingdom usually be referred for a barium meal. As a general rule patients with these symptoms would be seen first by their general practitioner, who would provide symptomatic treatment and review them again after about a month. If the symptoms persisted they would be investigated according to how the patient had responded. If the symptoms had settled they would be reassured and discharged; if they were still present a specialist ear, nose, and throat opinion, a chest X-ray, or an upper digestive endoscopy would have been requested. If it

[1]The comments by Professor Axon in this chapter were based on an assessment of the cases in December 2001 and his comments relate to Western practice at that time. Since then Japanese techniques have been embraced in the West with greater enthusiasm, particularly since the Paris classification was published* which was based on the Japanese macroscopic classification of early malignancy. As a result of this, Western endoscopists use chromoscopy more frequently than they did in the past and the number of centres performing endoscopic mucosal resection has risen.

*Endoscopic Classification Review Group (2005) Update on the Paris Classification of superficial neoplastic lesions in the digestive tract. Endoscopy 37:570–578

had been an upper digestive endoscopy it is likely in the UK that there would have been some delay in undertaking the procedure.

It is unclear from the history given why following the barium meal the patient was referred for upper gastrointestinal (GI) endoscopy. In the UK it is unlikely that endoscopy would have been requested unless an abnormality had been found on barium meal examination.

Endoscopic Appearance

The appearance of the stomach without dye spray appears to show evidence of chronic atrophic gastritis with intestinal metaplasia. No focal lesion is readily apparent. It is unlikely that dye spray would have been used in the West as this is not a routine procedure. It is possible that random biopsies would have been taken from the stomach.

Following dye spray there appears to be an oval lesion with a deeply stained base and slightly elevated hypostaining mucosa surrounding it. The stained appearances suggest a small ulcer. In retrospect the lesion may be apparent on close examination of the unstained photograph. Its nature is uncertain. Was this to be an early gastric cancer, I would agree that this appearance would be a IIc.

Histopathology

The Western pathologists in this case mainly reported high-grade dysplasia on the biopsy specimen. We know from experience that high-grade dysplasia is associated with invasive cancer in the majority of cases. In the UK this histology would have been reviewed with the histopathologists and with surgical colleagues, to come to a decision as to how to proceed.

Management

There is little experience in the West of endoscopic mucosal resection, and although this is being undertaken in a number of centers it is only within the last 2 or 3 years that endoscopists have been performing this procedure, usually in specialized centers. The most likely decision, therefore, would have been for a surgeon to be involved. It is likely that further endoscopy would have been requested with additional biopsies. Had this confirmed the abnormality, it is likely that total or subtotal gastrectomy would have been performed.

Summary

In summary, it is unlikely in the West that this patient would have been referred for endoscopy. Had endoscopy been done it is unlikely that the lesion would have been identified. Random biopsies would have been unlikely to have revealed the abnormality. Had it been revealed, total or subtotal gastrectomy would probably have been undertaken.

Endoscopy Commentary

Shigeaki Yoshida (Japan)

In conventional endoscopy (Fig. 1A), a small area of redness with a minute bleeding spot can be pointed out on the lesser curvature of the lower gastric body though it is tiny and ill demarcated. Because localized redness or discoloration is a very suggestive finding of malignancy [1, 2], additional dye-spraying endoscopy using indigo carmine (contrast technique) is necessary to disclose the details of the lesion. Actually, a dye-spraying picture (Fig. 1B) clarified a minute star-shaped depression surrounded by fold-like elevation, as a pooling of dye with a partially irregular border.

According to the Japanese diagnostic criteria, the irregularity (moth-eaten appearance) at the edge of the depression is highly suggestive of superficial cancerous invasion. The depressed lesion therefore requires a biopsy. On this occasion, even if the initial biopsy results were negative for malignancy due to its minimal size, an additional biopsy should be taken because of this very suspicious finding of malignancy under chromoendoscopy. When this lesion is confirmed as malignant or there is suspicion of malignancy histologically, it should be treated with endoscopic mucosal resection (EMR), because the size is estimated as only 5 mm or less which cannot be accompanied with metastatic lymph nodes.

Many Japanese investigators have compared macroscopic and histological features of a large number of depressed early cancers resected surgically or endoscopically, to establish the endoscopic diagnosis based on the histological evidence. As a result the following relationships between the two could be clarified. In those with ulcerative change within the cancerous lesion histologically [ul(+) carcinoma], gastric wall deformity and/or converging folds are characteristic endoscopic appearances even when the finding of ulceration in itself cannot be found endoscopically. In contrast, in those without histological ulceration [ul(–) carcinoma], marginal elevation without deformities is characteristic, endoscopically.

As to the histological type, the undifferentiated type is rarely found in minute or small cancers. The reasons are explained by the following evidence: firstly, the

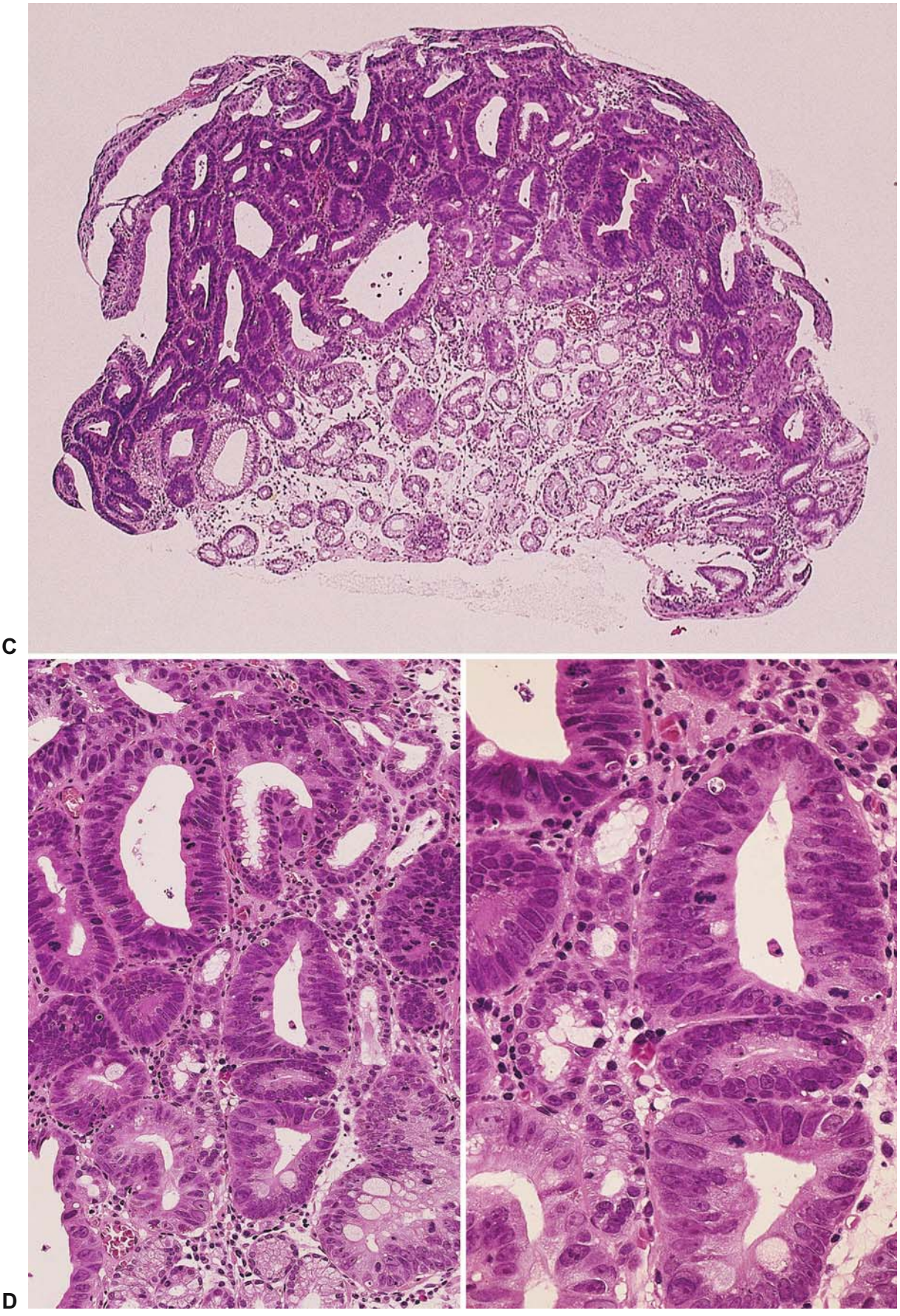
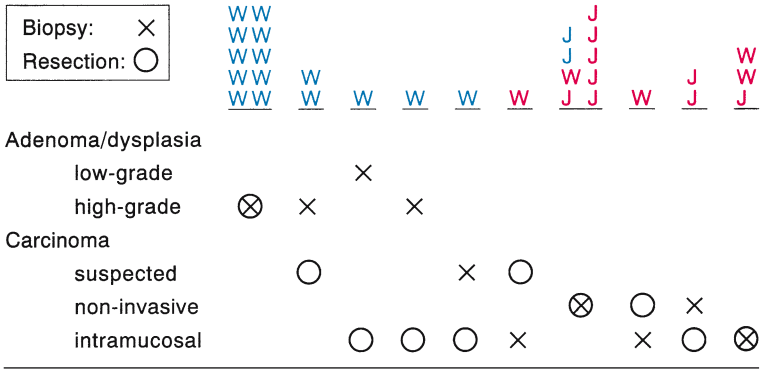


Fig. 1. **C** Biopsy specimen. **D** Detail of **C**. **E** Detail of **D**

Table 1. Gastric lesion 1



detection bias that arises because most minute cancers detected incidentally only show nonspecific findings, though several cases reveal faint monotonous discoloration endoscopically; and secondly, the histological metamorphosis from differentiated to undifferentiated types during the cancer development from a minute to conventional lesion, as shown by Saito et al [3].

In conclusion, the lesion presented can be diagnosed as a minute cancer of differentiated type without histological ulceration, and should be treated with EMR.

References

1. Yoshida S, Yamaguchi H, Tajiri H, et al (1984) Diagnosis of early gastric cancer seen as less malignant endoscopically. Jpn J Clin Oncol 14:225–241
2. Yoshida S, Yamaguchi H, Saito D, et al (1993) Endoscopic diagnosis; latest trends. In: Nishi M, Ichikawa H, Nakajima T, et al (eds) Gastric cancer. Springer, Tokyo, pp 246–262
3. Saito A, Shimoda T, Nakanishi Y, et al (2001) Histologic heterogeneity and mucin phenotypic expression in early gastric cancer. Pathol Int 51:165–171

Pathology Commentary

Manfred Stolte (Germany)

In the biopsy material obtained from the lesion, histological examination at low magnification (Fig. 1C) already clearly reveals a neoplastic rather than a regenerative change, since the normal foveolar architecture has been completely replaced by irregularly arranged, neoplastic tubuli. The diagnosis of neoplasia is confirmed under high magnification (Fig. 1D and E): the nuclei of the neoplastic epithelial cells are polymorphic and irregularly arranged, often hyperchromatic, and reveal an irregular chromatin structure, prominent nucleoli, and several abnormal mitotic figures. Based on these findings, the differential diagnosis lies between high-grade intraepithelial neoplasia (dysplasia) and well-differentiated tubular adenocarcinoma. Although no invasive tumor cells are definitely seen in the lamina propria, the highly irregular architecture of the densely packed neoplastic tubuli of varying caliber is no longer compatible with the budding and branching of a high-grade intraepithelial neoplasia. Rather, the invasive neoplastic tubuli clearly point to the histological diagnosis of a tubular adenocarcinoma.

The diagnosis of carcinoma is confirmed in the endoscopically resected specimen. At low power (Fig. 1F) the neoplastic tubuli are seen running perpendicular to the surface. On the edge of the tumor some show a parallel arrangement, suggestive of noninvasive neoplasia. However, the irregular architecture of the neoplastic tubuli, some aligned parallel to the muscularis mucosae as seen in the center of the tumor, clearly identify the lesion as an invasive carcinoma. This diagnosis is confirmed under higher magnification (Fig. 1G and H): the normal architecture of the surface structures of the gastric mucosa is completely disrupted. In high-grade intraepithelial neoplasia the architecture of the parallel arrangement of glands lined with neoplastic epithelial cells ought to be intact. However, here again we see densely packed, irregularly arranged invasive neoplastic tubuli of varying caliber. The cytological criteria for an adenocarcinoma are also met.

In conclusion, there is no doubt that the diagnosis is invasive intramucosal well-differentiated adenocarcinoma, established in both the biopsy and endoscopic mucosectomy specimens.

Western pathologists often underdiagnose intramucosal well-differentiated adenocarcinoma as high-grade dysplasia, in this particular case by ten of the Western pathologists. Four other Western pathologists then corrected their biopsy-based dysplasia diagnosis on

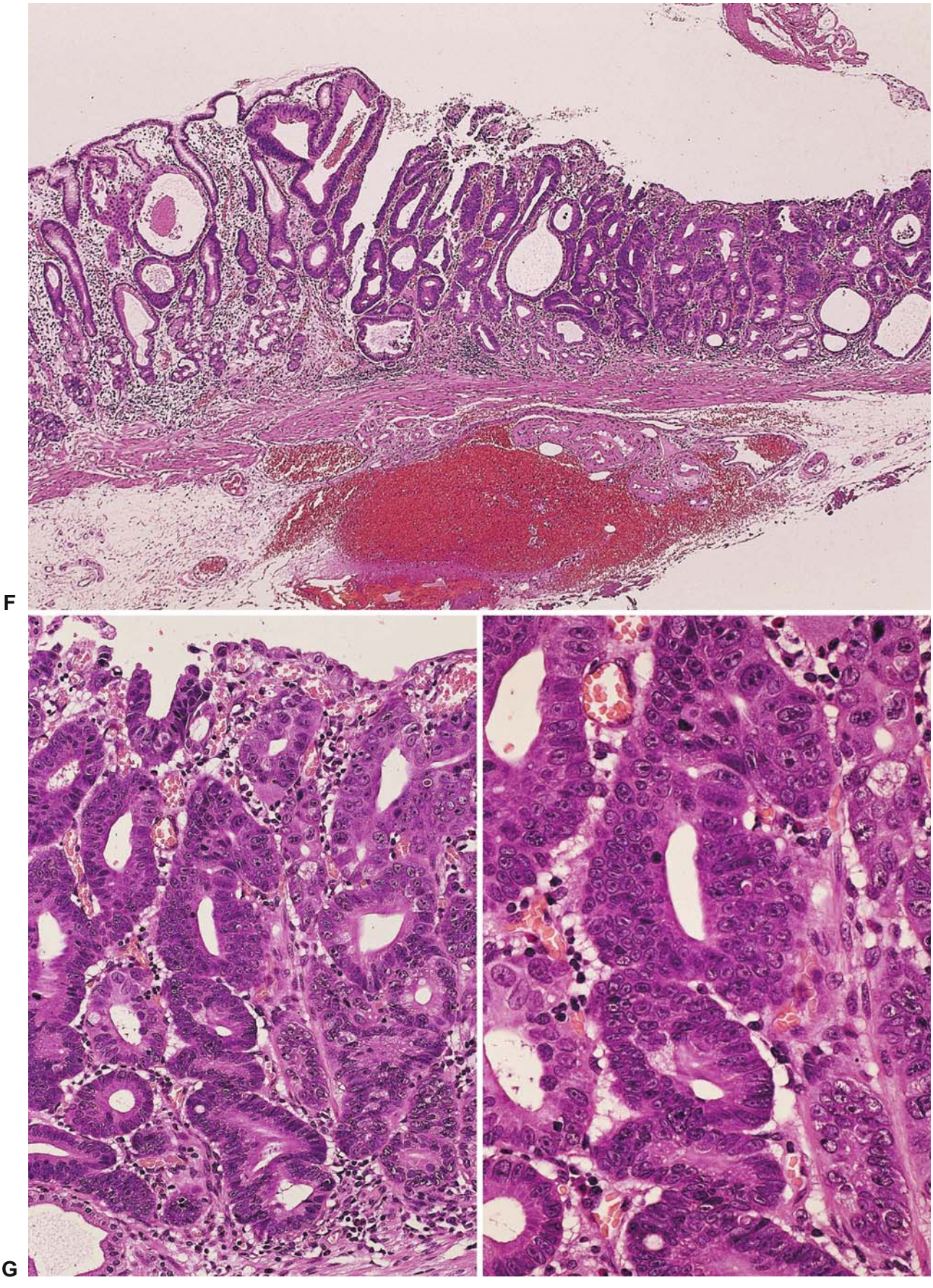


Fig. 1. **F** Endoscopically resected specimen. **G** Detail of **F**. **H** Detail of **G**

interpreting the mucosectomy specimen. In common with all the Japanese pathologists, however, six Western pathologists made the correct carcinoma diagnosis.

Pathology Commentary

Yo Kato (Japan)

The low-power view of the biopsy specimen shows an aggregate of slightly irregular-shaped round or tubular glands in the upper half of the mucosa (Fig. 1C). The glands consist of columnar cells with a swollen oval nucleus and a high N/C ratio accompanied by moderate nuclear pseudostratification (Fig. 1D). The nuclei are vesicular, containing one or two prominent nucleoli, and the mitoses are remarkable (Fig. 1E). Non-neoplastic glands with small nuclei are interspread among the neoplastic glands. Since the invasion is not clear, the change corresponds to noninvasive carcinoma from the Japanese viewpoint, to be classified as category IV in the Vienna classification (Fig. 1F).

In the endoscopic mucosal resection (EMR) specimen, the tubular tumor with occasional dilated glands is completely limited to the mucosa, occupying its full thickness in the right half of the figure (Fig. 1F). The slightly irregular tubular glands are composed more of cuboidal cells with a swollen round nucleus than in the biopsy specimen. (Fig. 1G). Round nuclei with one or two dark eosinophilic nucleoli are prominent (Fig. 1H). Similar to the biopsy specimen, the invasion is not clear, therefore noninvasive carcinoma is considered to be the proper diagnosis also for the EMR specimen, i.e., category IV by the Vienna classification (Fig. 1F).

Case 2, IIc

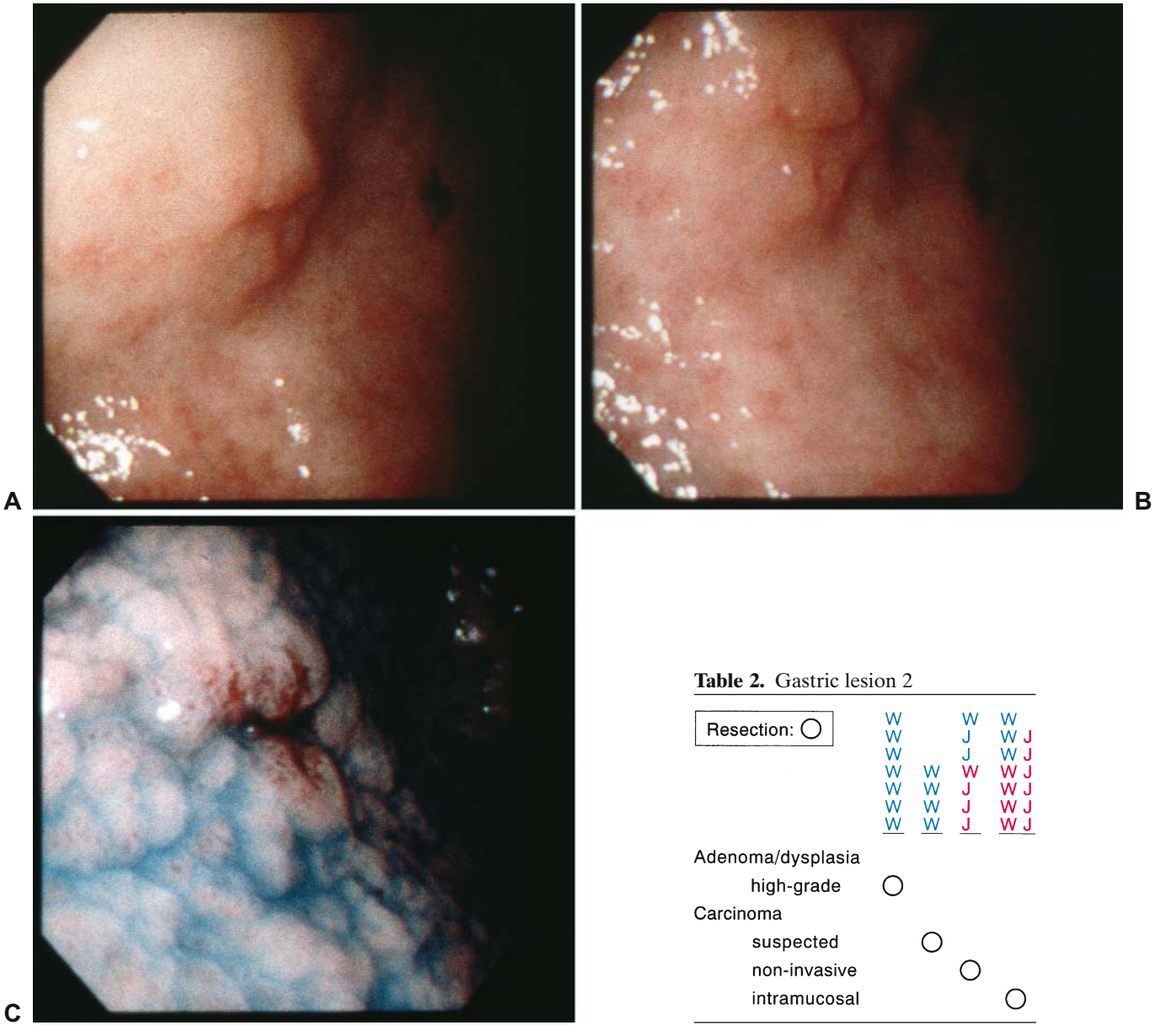


Table 2. Gastric lesion 2

Resection: ○	W W W W W W W	W W W	W J J W W J J	W W J J J J J
Adenoma/dysplasia				
high-grade	○			
Carcinoma				
suspected		○		
non-invasive			○	
intramucosal				○

Fig. 2. **A** Angulus, anterior wall. **B** Same site. **C** Same site after spraying indigo carmine

Case Description

A man, aged 78 years, with a history of pulmonary emphysema, complained of mild anorexia for a month and underwent an upper GI endoscopic examination. A lesion of 7 mm in diameter was found at the anterior wall side of the angulus and was biopsied. One month later, endoscopic ultrasonographic examination and, on the following day, endoscopic resection were performed. The resection margins were free of tumor. On follow-up endoscopic examinations, no local recurrence was found.

Endoscopy Commentary

Anthony T.R. Axon (UK)[1]

History

A man of 78 years with a month's history of mild anorexia would have attended his general practitioner, who would have taken a history, and would have been unlikely to have referred the patient for endoscopy unless there had been some weight loss or other reason for referring for a gastrointestinal opinion. It is likely that some blood tests and chest X-ray would have been undertaken and the patient would have been reviewed following the results of these tests. If the symptoms of anorexia had persisted he would probably have been referred for a medical opinion at the hospital, where a specialist would have undertaken further investigations and probably referred him for upper digestive endoscopy.

Endoscopic Appearance

The upper digestive endoscopy shows a protuberant lesion in the stomach close to the angulus. The stomach appears to have significant chronic gastritis and intestinal metaplasia. The appearance arouses suspicion of an early carcinoma and would, I think, have been detected by a Western endoscopist. Biopsies would have been taken from the lesion. As the lesion is protuberant it is unlikely that this would have been classified in the West as a IIc. It is more likely that a Western endoscopist would have classified it as a I, if requested to classify it. In the West, however, endoscopists do not commonly use the Japanese classification when reporting endoscopic appearance. We have little first-hand experience with early gastric cancer, the majority being identified as such only after resection of type III lesions.

Histology

The biopsy report in this case is not available, only the resection specimen; however, the appearances of the resection specimen were, according to Western pathologists, highly suggestive of high-grade dysplasia or carcinoma.

Management

It is possible that in some specialized centers endoscopic ultrasound would have been performed here; however, a combination of the macroscopic appearance with the suspicious histology would have led to surgical referral. It is likely that the final decision would have been that this was a cancer, and resection of the distal stomach would have been undertaken.

Summary

It is likely that there would have been a greater delay in the time taken for endoscopy to be performed. It is probable that the lesion would have been diagnosed as cancer and that distal gastric resection would have been performed.

Endoscopy Commentary

Shigeaki Yoshida (Japan)

A depressed lesion around less than 10 mm in size (corresponding to the diameter of two or three granules of *areae gastricae*) is located in the anterior wall of the lower gastric body or angulus. The endoscopic finding grossly consists of a star-shaped depression and surrounding elevated components, as shown in Fig. 2A. A conventional endoscopic picture in close-up view (Fig. 2B) discloses the irregularity in the margin of the depressed area and the typical moth-eaten appearance indicating definite malignancy.

The questions raised are how to perform macroscopic typing and how to estimate the degree of vertical invasion. The answers should entirely depend on whether we consider the elevated components as a result of cancerous invasion or of benign inflammatory changes. In this respect, a dye-spraying picture (Fig. 2C) gives us useful information that the appearance of the elevated components is mostly the same as the surrounding granular lesions (boiled-rice appearance) of intestinal metaplasia, although some erosive changes are detectable at the border of the depression. In addition, since elevated early cancers usually show lustrous and hyperemic appearances under dye-spraying endoscopy, the elevated components in this case are estimated to be the result of hyperplastic changes of metaplastic mucosa, rather than neoplastic growth. Also, the surrounding elevated component is not so dominant, so that this lesion can be classified macroscopically into not IIa+IIc, but IIc type.

The target findings best known to estimate submucosal invasion in general are swelling of tips of converging folds and fusion of folds. The dye-spraying picture fails to reveal such folds. The invasion should be limited, also because the lesion presented is not accompanied with slow-sloped elevation, as in a submucosal tumor, due to deep invasion.

As to the histological type, the hyperemic appearance in the depressed area whose margin is vaguely defined

[1]See footnote on p. 4.

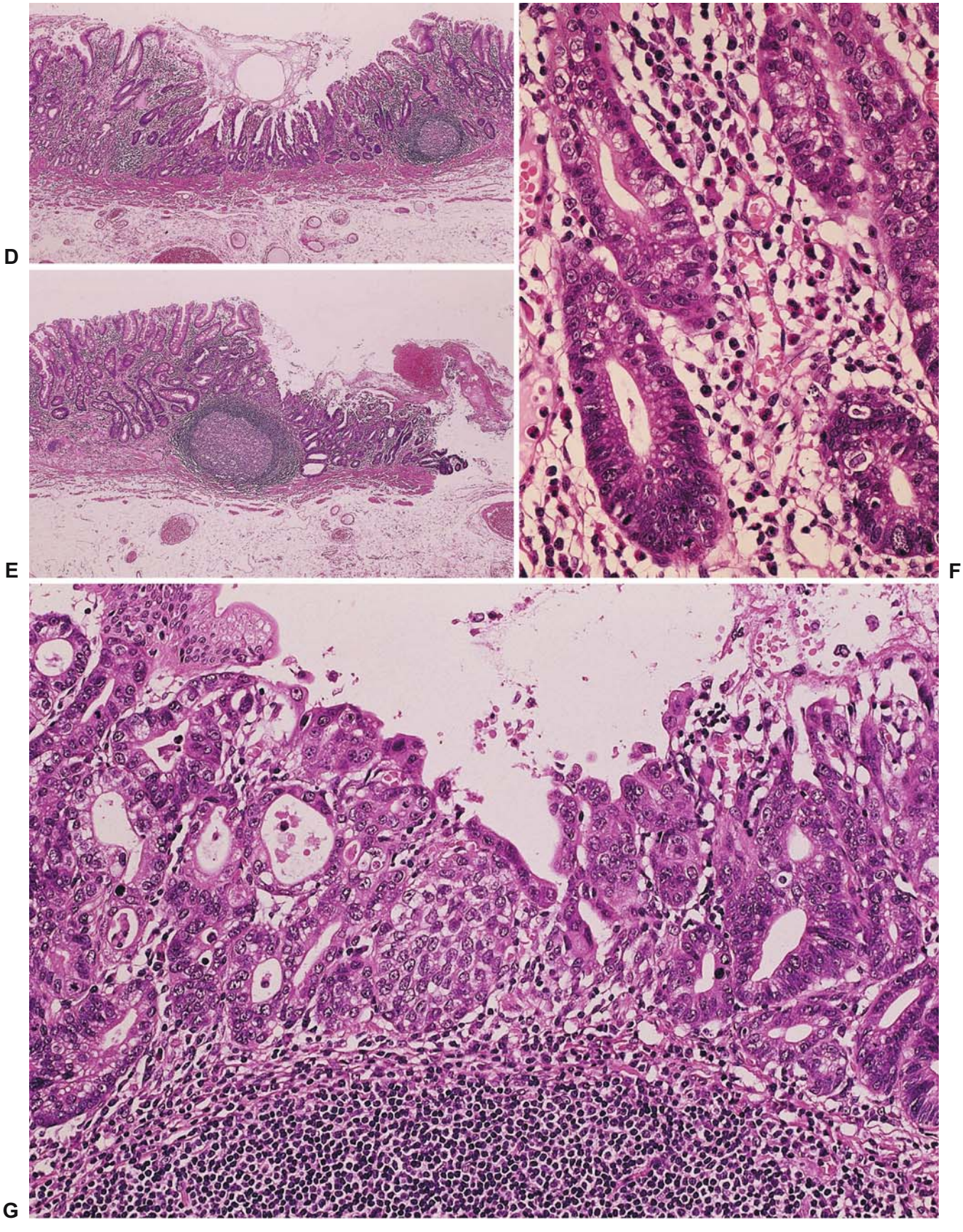


Fig. 2. **D** Resected specimen. **E** Other section of same specimen. **F** Detail of **D**. **G** Detail of **E**

is suggestive of the differentiated type, since the undifferentiated type usually shows a discolored depression with a sharply defined margin.

In conclusion, the final endoscopic diagnosis of this lesion should be a IIc type of early gastric cancer with a low probability of submucosal invasion, of the differentiated type.

Since in Japan EMR is usually indicated for mucosal cancers of the differentiated type less than 2 cm without histological ulceration [1] in order to guarantee the absence of metastasis, this lesion appears to have an absolute indication for EMR. Also, when the resected specimen histologically reveals that the cancerous invasion is limited to within the mucosal layer without any components of vascular invasion, the treatment result can be regarded as curative regardless of histological type and histological ulceration, according to the criteria of Yamao et al [2].

References

1. Yoshida S (1997) Endoscopic treatment. In: Saugimura T, Sasako M (eds) Gastric cancer. Oxford University Press, Tokyo, pp 252–262
2. Yamao T, Shirao K, Ono H, et al (1996) Risk factors for lymph node metastasis from intramucosal gastric carcinoma. Cancer 77:602–606

Pathology Commentary

Manfred Stolte (Germany)

The endoscopic appearance alone (Fig. 2A–C) strongly suggests that the lesion is a type IIc early gastric carcinoma and not a benign lesion. The overview of the endoscopic mucosectomy specimen already reveals that the small lesion with its central depression is a well-differentiated intramucosal invasive tubular adenocarcinoma. The numerous densely packed, relatively small neoplastic tubuli located immediately above the muscularis mucosae are no longer compatible with a high-grade intraepithelial neoplasia, but are a result of invasion of these tubuli into the lamina propria. In the margin of the carcinoma, chronic active *Helicobacter pylori* gastritis with intestinal metaplasia and lymphoid follicles—the soil in which the early carcinoma developed—can be seen. Additional evidence for carcinoma is the superficial erosion in the center of the lesion indicating destructive growth (Fig. 2E).

The section of the lesion seen in high power view (Fig. 2F) does not permit a differentiation between an invasive carcinoma and high-grade dysplasia. Figure 2G, however, again shows the irregular pattern of the densely packed invasive tubuli and also, clearly recognizable, an invasive tumor sliver.

In conclusion this case is, without any doubt, a type IIc early carcinoma limited to the mucosa and histologically classifiable as a well-differentiated tubular adenocarcinoma.

The correct diagnosis of carcinoma was established not only by all the Japanese, but also by 13 Western pathologists. Only seven Western pathologists made the underdiagnosis of high-grade dysplasia.

Pathology Commentary

Yo Kato (Japan)

Only the resected specimen is available in this case. The erosive lesion shown in the center of Fig. 2D and in the center to right part of Fig. 2E consists of short glands and medium-sized to small glands, which are limited to the mucosa.

The glands are anastomosing irregularly in part (Fig. 2D, right and middle-left), and compacted in other parts (Fig. 2E). With these patterns, it is not difficult for Japanese pathologists to diagnose the lesion as carcinoma, moderately differentiated tubular carcinoma [tub 2 according to the Japanese Research Society for the Study of Gastric Cancer (JRSGC) classification], but for some glands included in the lesion as shown at least in Fig. 2F it is actually difficult to give a definite diagnosis.

However, the epithelia harboring relatively vesicular and swollen nuclei with a prominent nucleolus are findings suggestive of carcinoma (noninvasive carcinoma so far as the figure is concerned). As to whether the lesion is invasive or noninvasive, since small glands budding or sprouting from the medium-sized glands exist, an invasive lesion is strongly suggested (Fig. 2G). The atypical glands of Fig. 2G correspond in total to tub 2.

Here, the epithelia form a solid nest as well (Fig. 2G, center) and the lesion is generally associated with more remarkable cellular or nuclear atypias than those of atypical glands of Fig. 2F in terms of vesicular and swollen nuclei with a prominent nucleolus. These are the findings on which most Japanese pathologists base their diagnosis of carcinoma even without evident invasive patterns.

Looking at Table 2, I imagine that the differential diagnosis between invasive and noninvasive carcinoma is difficult, not only for Japanese pathologists who are not accustomed to doing it but also for Western pathologists for whom it is obligatory routinely for a diagnosis of carcinoma.

Case 3, IIc

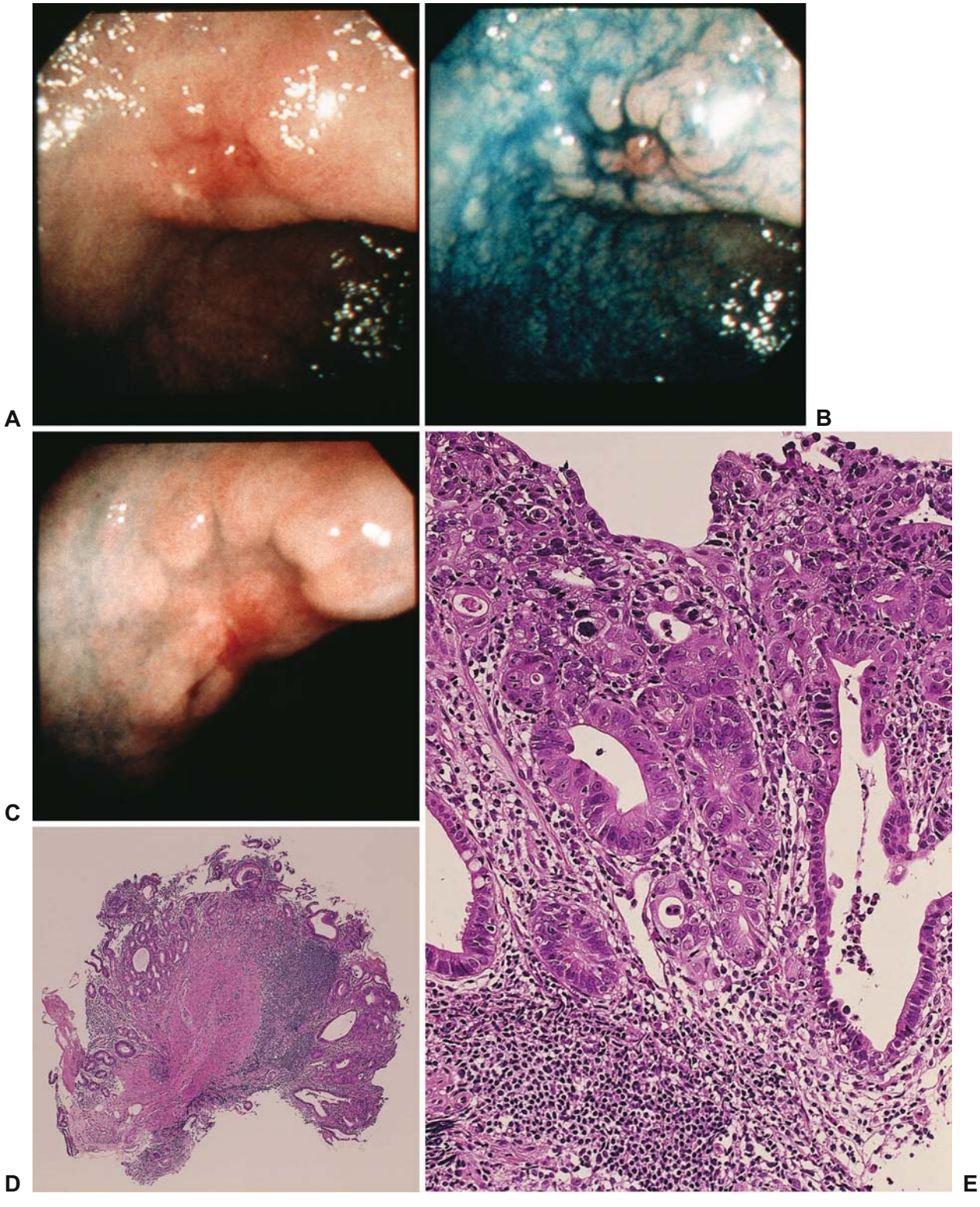


Fig. 3. **A** Angulus, anterior wall. **B** Same site after spraying indigo carmine. **C** Close-up view. **D** Biopsy specimen. **E** Detail of **D**

Case Description

A man, aged 76 years, with a history of myocardial infarction, cerebral infarction, and congestive heart failure, underwent upper GI screening by endoscopic examination. A lesion of 12 mm in diameter was found at the anterior wall side of the angulus and was biopsied. A week later endoscopic resection was performed. The resection margins were free of tumor.

Endoscopy Commentary

Anthony T.R. Axon (UK)[1]

History

As this was a 76-year-old man with serious general medical problems, he would not have been referred for endoscopic examination in the West unless he had complained of symptoms referable to his upper GI tract. The lesion in the stomach therefore would not have been identified.

Endoscopy

In the event that endoscopy had been carried out for some reason, the sizable lesion proximal to the angulus would have been identified. The appearances are those of an ulcer with an elevated circumferential margin, irregular in appearance and highly suspicious of cancer. It is unlikely that dye spray would have been used, but multiple biopsies would have been taken from the area.

Histology

The biopsies by Western pathologists were in agreement that there was high-grade dysplasia or worse. Only one pathologist suggested that it might be low-grade dysplasia. On this basis a diagnosis of cancer would have been made.

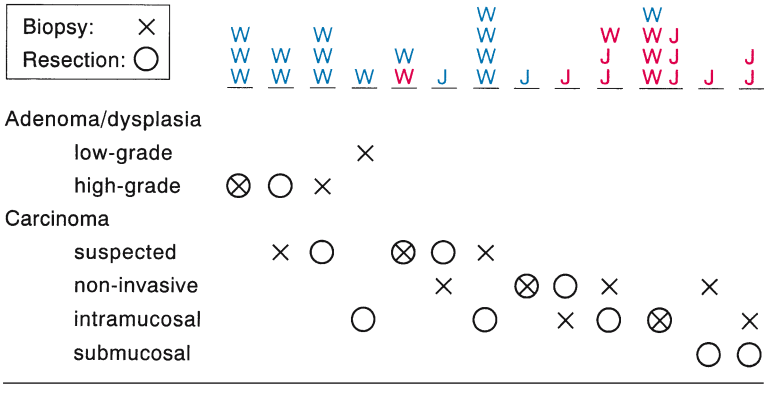
Management

A surgical opinion would have been requested and this would have led to a problem because the patient had sustained a myocardial infarction, a cerebral infarction, and was in congestive heart failure. So although the surgeon would have been inclined to carry out a gastric resection, the advice of an anesthetist would have been sought. If it was considered that the patient was suitable for major surgery, an operation would have been performed. If the anesthetist had felt that the patient would be unlikely to survive surgery, the implication would have been that he would be more likely to have died from his general medical condition than the carcinoma itself so, after discussion with the patient and the relatives, palliative care would have been given. With the introduction of endoscopic mucosal resection in the West, today it is possible the patient might have been sent to a tertiary referral center where endoscopic mucosal resection might have been performed.

Summary

In this case the lesion would not have been diagnosed because the patient would not have been referred for endoscopy in the first place. Had the lesion been identified it would have been resected, if the patient was fit enough to undergo the procedure; otherwise palliative

Table 3. Gastric lesion 3



[1]See footnote on p. 4.

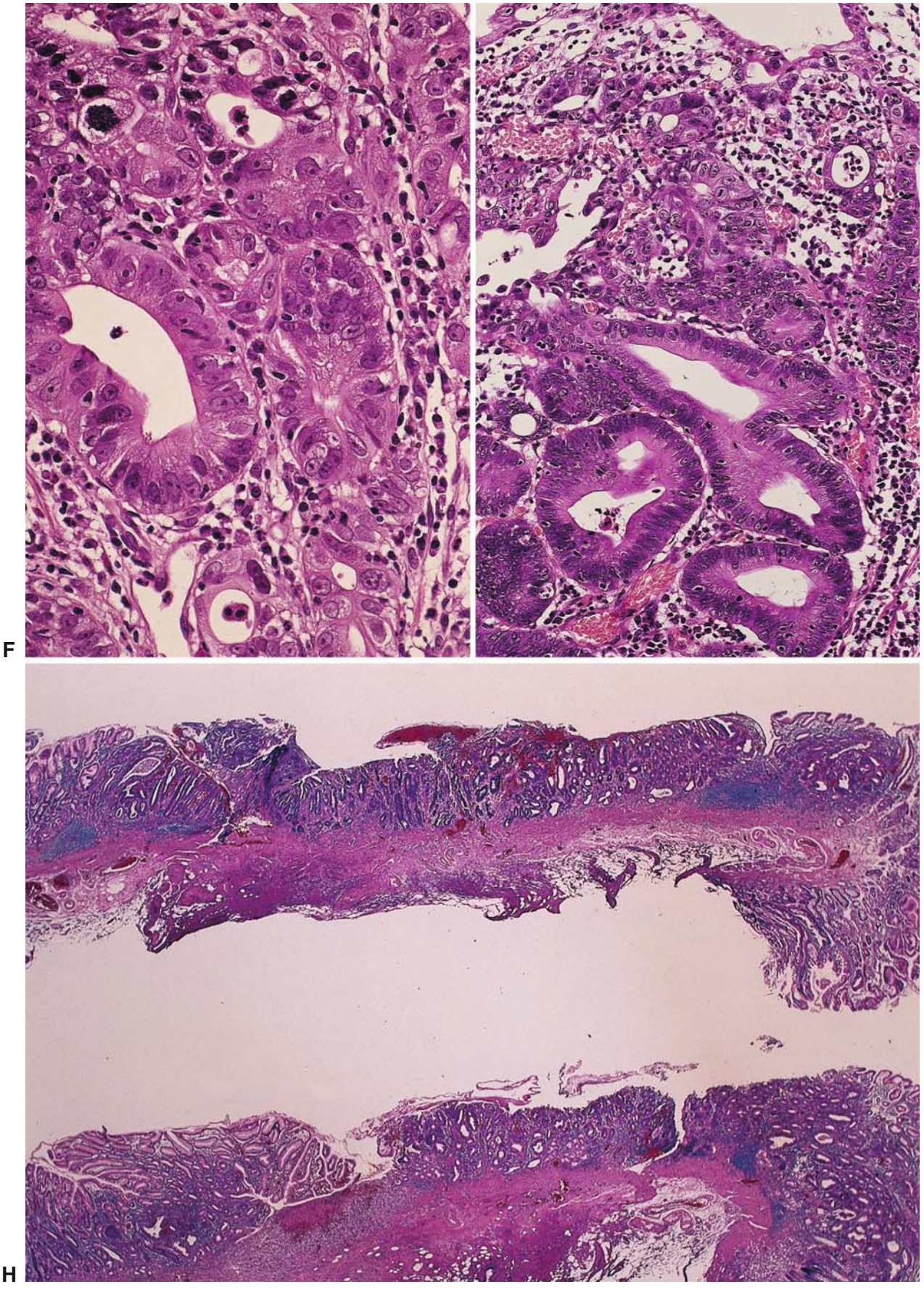


Fig. 3. **F** Detail of **E** (biopsy). **G** Detail of resected specimen. **H** Resected specimen overview

care or referral to a tertiary center may have been undertaken.

Endoscopy Commentary

Shigeaki Yoshida (Japan)

A lesion of around 10–15 mm in size is located on the lesser curvature of the angulus. Endoscopically, it is seen as a superficial depression surrounded by thickened mucosa, which is actually formed by the swollen tips of converging folds (ul(+) lesion). In addition, granular lesions ("islet formation") are seen within the depressed area (Fig. 3A). The malignancy of the lesion is easily suspected from the irregularity of the depressed margin, particularly the moth-eaten appearance detected at the tip of the fold as shown in Fig. 3C, and macroscopic typing of IIc is also easy to make, because the surrounding elevated components are not remarkable macroscopically.

The question is whether the lesion has deeper invasion. Dye-spraying pictures (Fig. 3B and C) show two contradictory findings. One is that tips of folds are separated from each other, indicating little possibility of deeper invasion, and the other is the presence of a conspicuous granular lesion within the depression, indicating no small possibility of deeper invasion although it should be limited. As a preoperative diagnosis that has to assume the worst, therefore, we should accept the possibility of deeper invasion in this case.

As to the estimation of the histological type, this lesion showed characteristics of both differentiated and undifferentiated types, the former being the lustrous hyperemic appearance of the depressed area and the latter the sharply demarcated margin of the depression. Hence, it is difficult to estimate the histological type in this case.

In conclusion, this lesion can be diagnosed endoscopically as a IIc type of early cancer [ul(+) carcinoma] with possible submucosal invasion, of which the histological type is unknown.

Endoscopic mucosal resection can be indicated for this lesion as an optional choice when the depressed area is lifted up well by saline injection (negative for "nonlifting sign"), since the size is estimated to be around 10–15 mm, fold convergence is not remarkable in dye-spraying pictures, and the surrounding elevation is not suggestive of massive submucosal invasion endoscopically.

Pathology Commentary

Manfred Stolte (Germany)

The endoscopic appearance (Fig. 3A–C) alone shows that this lesion is not a benign lesion but must be a type IIc gastric carcinoma. This is already confirmed histologically in the biopsy specimen. The low-power view (Fig. 3D) suffices to establish the diagnosis of carcinoma on the basis of the irregular architecture of the neoplastic tubuli. This is impressively confirmed in Fig. 3E, which clearly shows aggregations of densely packed invasive tumor cells at the surface near the neoplastic tubuli. This is also confirmed under higher magnification (Fig. 3F and G). Invasive neoplastic glands with polymorphic nuclei with irregular chromatin, prominent nucleoli, and abnormal mitotic figures are seen, as well as unmistakable individual carcinoma cells that have separated from the tubuli in the adjacent lamina propria.

In the endoscopic mucosectomy specimen (Fig. 3H), the overview shows that the carcinoma is limited to the mucosa. Adjacent to the carcinoma the underlying disease, chronic active *H. pylori* gastritis, can be seen.

In this case, only three Western pathologists were of the opinion that this lesion was merely a high-grade dysplasia. Three other Western pathologists corrected their biopsy-based high-grade dysplasia diagnosis on examining the mucosectomy specimen, while all the remaining Western pathologists together with all the Japanese pathologists diagnosed carcinoma.

Pathology Commentary

Yo Kato (Japan)

The biopsied mucosa is covered by atypical glands of various sizes, particularly on its right side (Fig. 3D). The atypical glands consist mostly of eosinophilic cuboidal cells with a pale, round to oval, swollen nucleus with a prominent nucleolus (Fig. 3E,F). Some small glands seem to start invading the lamina propria mucosae. The nuclear hyperchromasia seen in the right ends of the pictures (Fig. 3E,F) may be due to the artifacts related to the biopsy procedure. One nucleus corresponds clearly to mitosis. With the above findings, an invasive, moderately differentiated adenocarcinoma (tub 2) is considered, but there exists also a part corresponding to very well-differentiated carcinoma (tub 1) composed of columnar cells with a basally situated hyperchromatic round to oval nucleus (Fig. 3G, lower half).

The pathological examination of the EMR specimen revealed that the carcinoma was limited to the mucosa and was completely resected.

Case 4, IIa+IIc

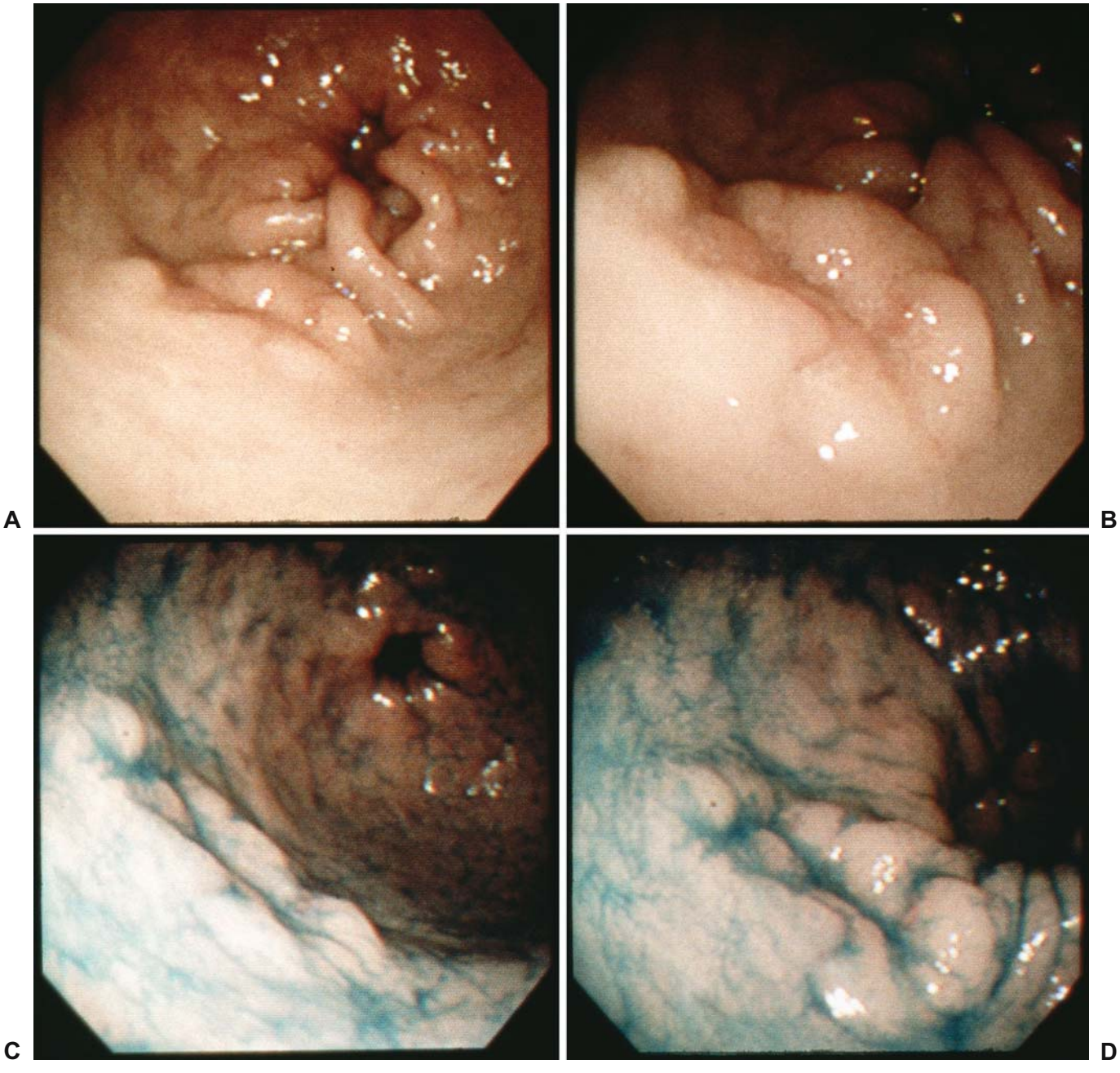


Fig. 4. **A** Antrum, anterior wall. **B** Close-up view. **C** Same site after spraying indigo carmine. **D** Close-up view

Case Description

A woman, aged 76 years, with diabetic nephropathy and normocytic anemia, had no dyspeptic symptoms but underwent upper GI screening by endoscopy. A lesion of 17 mm in diameter was found at the anterior wall of the antrum and was biopsied. Three weeks later endoscopic resection was performed. The resection margins were free of tumor.

Endoscopy Commentary

Anthony T.R. Axon (UK)[1]

History

This 76-year-old woman would not have been referred for endoscopy because GI screening for cancer is not normally undertaken in the West.

Endoscopy

Had endoscopy been undertaken, it would therefore have been for symptoms and the examination would have been orientated towards identifying a cause of the symptoms rather than seeking evidence of cancer. Had the procedure been undertaken for non-specific dyspepsia, it is probable that the lesion would not have been identified because it is set among rugosal folds. There is no abnormality of color and no ulceration. Had dye spray been used (and this is unlikely), the lesion would probably have been identified because after indigo carmine, the lumen is more distended, the folds have disappeared, and the lesion stands out more obviously. It is possible that it would have been seen without the indigo carmine if the stomach had been distended to a greater degree on the earlier photographs. Had it been recognized it would be seen to be a largish lesion, and biopsies would have been taken from it.

Histology

The Western pathologists have reported the lesion as likely to be a carcinoma and under these circumstances, a surgical referral would have been undertaken and the patient would have been subjected to total gastrectomy.

Summary

This lesion would not have been identified in the West because the patient would not have been referred for endoscopic screening for cancer. Had the lesion been identified, total gastrectomy would probably have been undertaken.

Endoscopy Commentary

Shigeaki Yoshida (Japan)

A depressed lesion surrounded by annular-form elevation is located in the anterior wall of the antrum. The size of the lesion is estimated to be around 20 mm. In conventional endoscopy, this is seen as a superficial depression surrounded by a worm-like elevation whose surface is smooth and lustrous, similar to gastric adenoma. The definite finding of the moth-eaten appearance can be pointed out particularly at the greater curvature side, as shown in Fig. 4A and B. Dye-spraying pictures (Fig. 4C and D) reveal fold-like components within the depressed area and, in particular, Fig. 4D demonstrates the irregular margin of the depression indicating the definite malignancy of the lesion.

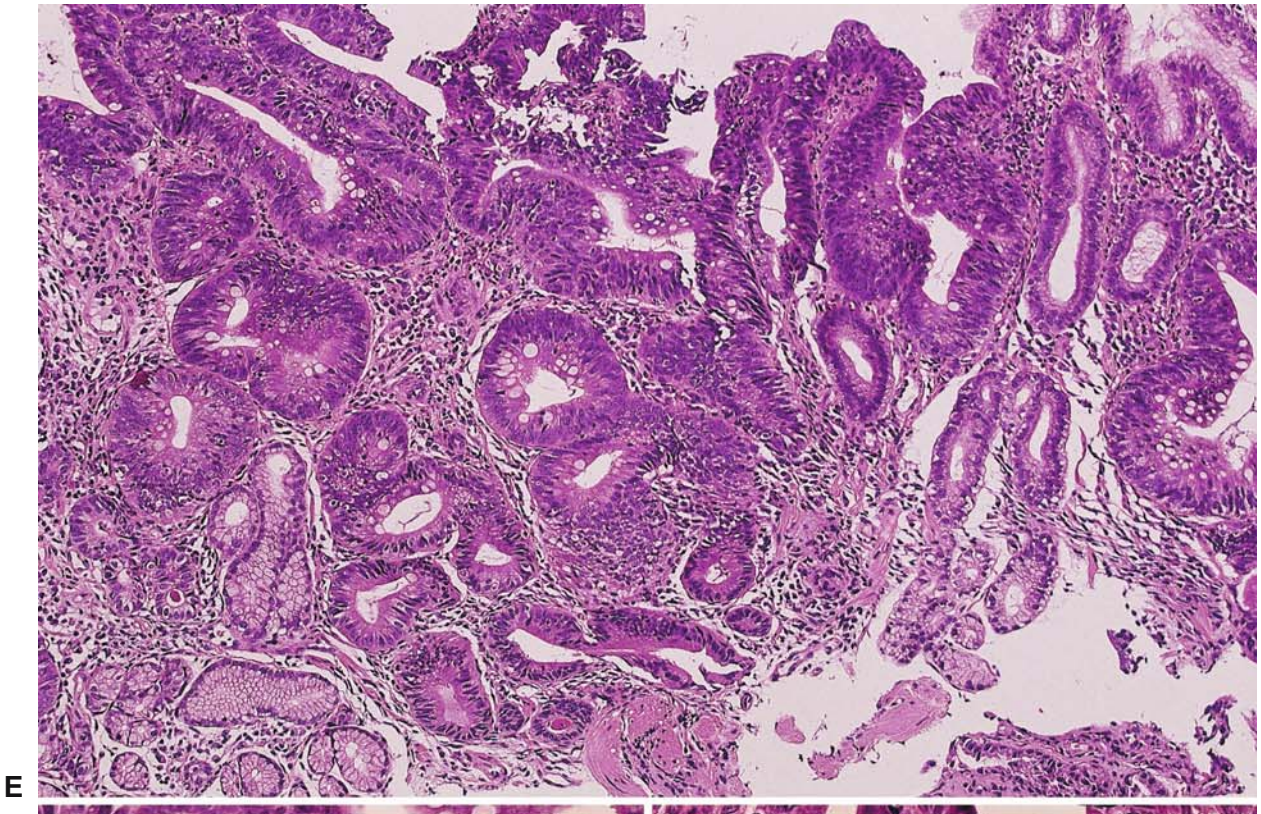
The first question is which macroscopic type is more likely, IIa+IIc or IIc, because marginal elevation is not only seen in type IIa+IIc but occasionally in type IIc. In spite of this, type IIa+IIc appears to be more acceptable for the lesion presented, because the marginal elevation is obviously and constantly seen regardless of whether pictures are from conventional or dye-spraying endoscopy. In addition, fold-like elevation within the depressed area may indicate that this lesion is essentially an elevated lesion.

The second question is whether the lesion accords with submucosal (or much deeper) invasion. In the case of type IIa+IIc being deeply invasive, the following suggestive findings are usually detectable: (1) deep and destructive depression, (2) annular formation due to fusion of elevated components, (3) slow-sloped elevation surrounding the depressed area, and/or (4) converging folds due to disturbance of elasticity of the gastric wall by massive deeper invasion. In this lesion, however, the above findings are not detected at all and elevated components seen in the depressed area, meaning less destruction, should indicate a very low probability of submucosal invasion.

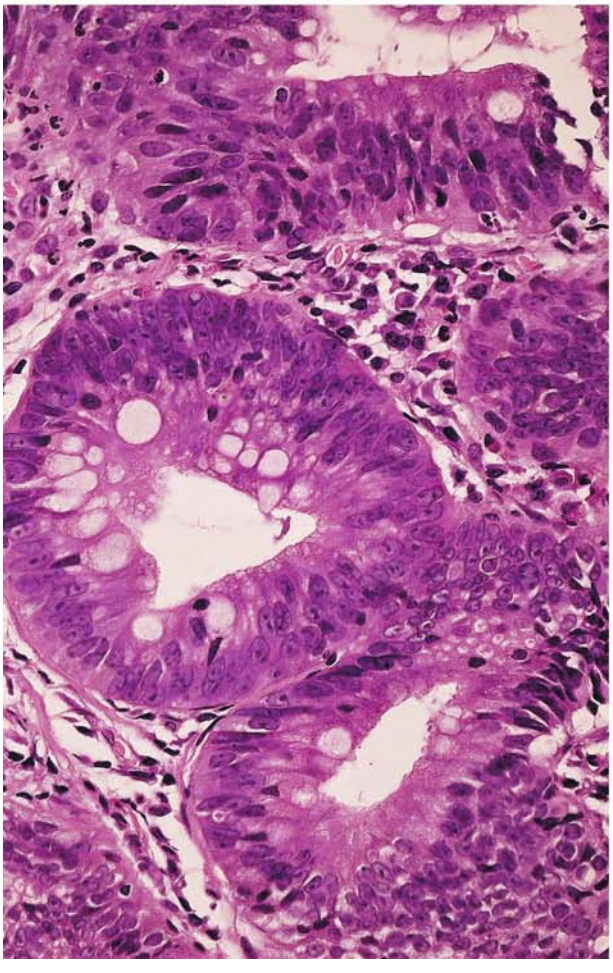
As to the histological type, hyperemic and smooth-surfaced appearances in the depressed area, in addition to fewer eroded components in the elevated component, are the findings being highly suggestive of the differentiated type of tubular adenocarcinoma.

In conclusion, this lesion can be diagnosed as a nonulcerative IIa+IIc type of early cancer being of differentiated type histologically, whose invasion is limited to within the mucosal layer.

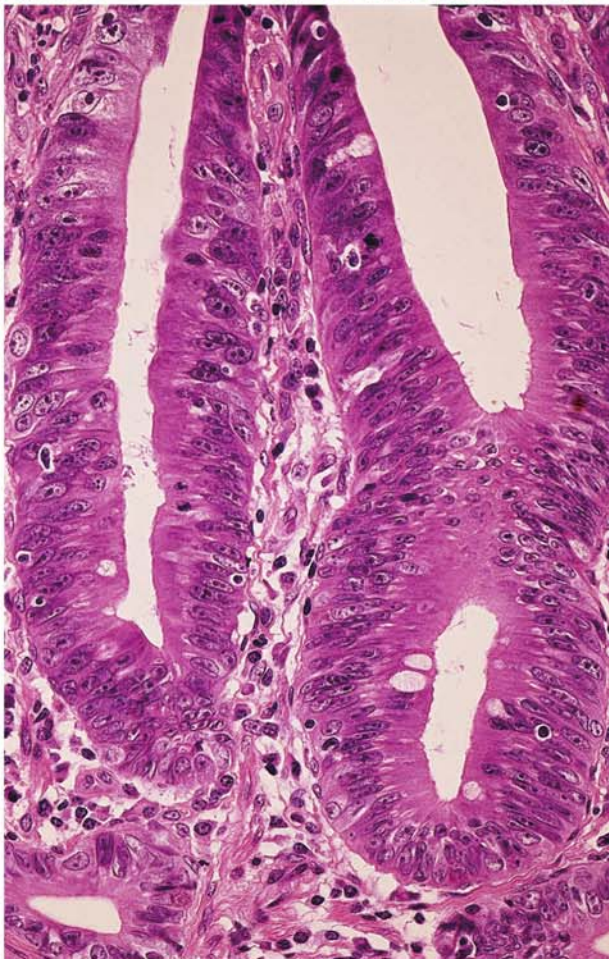
[1]See footnote on p. 4.



E



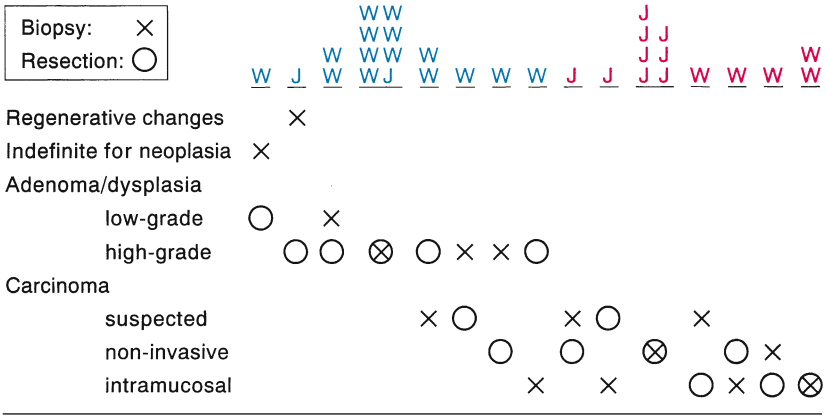
F



G

Fig. 4. **E** Biopsy specimen. **F** Detail of **E** (biopsy). **G** Detail of resected specimen

Table 4. Gastric lesion 4



Endoscopic mucosal resection can be selected for the treatment of this lesion, i.e., a differentiated type of early cancer with a very low possibility of submucosal invasion. Considering the size being around 20 mm in diameter, however, conventional strip biopsy [1] appears to be a difficult approach to make a one-segment resection because of the limitation in size of the snare loop. In such cases, our newly developed EMR using an IT-knife should be useful, as previously reported [2, 3].

References

1. Tada M, Karita M, Yanai M (1987) Treatment of early gastric cancer using strip biopsy: a new technique for jumbo biopsy. In: Takemoto T, Kaeai T (eds). Recent topics of digestive endoscopy. Excerpta Medics, Tokyo, pp 137–142
2. Yoshida S (1998) Endoscopic diagnosis and treatment of early cancer in the alimentary tract. Digestion 59:502–508
3. Ono H, Kondo H, Gotoda T, et al (2001) Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 48:225–229

Pathology Commentary

Manfred Stolte (Germany)

Examination of the biopsy specimen from this lesion leaves no doubt as to the diagnosis of neoplasia. The nuclei of the tumor cells in the neoplastic tubuli manifest an irregular arrangement, contain an irregular chromatin structure and prominent nucleoli, and show abnormal mitotic figures (Fig. 4F).

The differential diagnosis includes high-grade dysplasia, noninvasive carcinoma, or an intramucosal carcinoma. In my opinion, however, clear criteria for the diagnosis of invasive intramucosal carcinoma are to be seen in Fig. 4E, which shows not only disruption of the normal glandular architecture of the antral mucosa, but also a horizontal invasive neoplastic tubule parallel to the muscularis mucosae. A further criterion for invasion is the finding of tiny glandular structures in the vicinity of this tubule.

In the endoscopic mucosectomy specimen (Fig. 4H, I, and G), the predominantly parallel arrangement of neoplastic glands running perpendicular to the surface suggests that this lesion might be "only" high-grade intraepithelial neoplasm or noninvasive carcinoma. Evidence for intramucosal carcinoma, however, is again the atypical neoplastic branches in the left margin of the lesion, and several tiny neoplastic glands that can be seen at the base of the lesion.

In conclusion I would diagnose, both in the biopsy material and the endoscopic mucosectomy specimen, a well-differentiated tubular adenocarcinoma limited to the mucosa.

The spectrum of diagnoses in this case is unusually wide. Most Western pathologists and two Japanese pathologists diagnosed only dysplasia—mostly high-grade dysplasia—while the majority of the Japanese pathologists opted for noninvasive carcinoma, and four of the other Western pathologists diagnosed an intramucosal carcinoma on the basis of the criteria mentioned above.

Pathology Commentary

Yo Kato (Japan)

The biopsy specimen indicates that the lesion consists of immature intestinal-type tubular glands, which are slightly irregularly distributed and contain a fair number of goblet cells. The lamina propria mucosae is

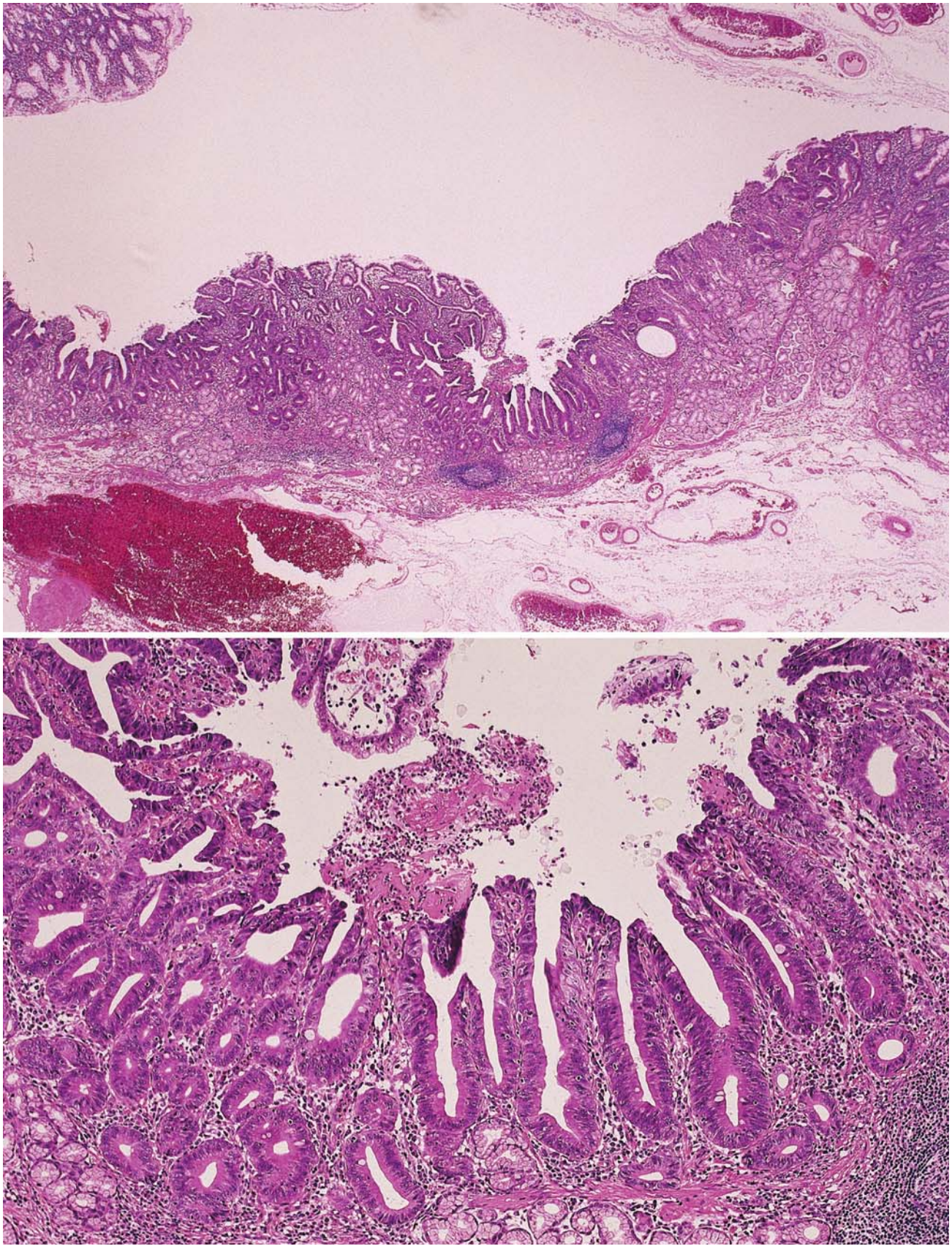


Fig. 4. **H** Resected specimen. **I** Detail of **H**

infiltrated with inflammatory cells. Because of the presence of slightly irregular-shaped glands with nuclear stratification in the surface of the lesion, or loss of maturation from the bottom toward the top of the glands, the change is judged as group IV, i.e., suspicion of very well-differentiated tubular carcinoma according to the Japanese classification: the change will correspond to adenoma/dysplasia of high-grade from a Western viewpoint. Figure 4F is a magnification of the center of Fig. 4E, showing round glands with crowded ovoid plump nuclei situated along the basement membrane and the epithelium, with disoriented similar nuclei in the surface of the lesion.

The EMR specimen shows a small depressed lesion (Fig. 4H), which consists of short, straight tubular or round glands (Fig. 4I). Each gland is composed of eosinophilic, tall columnar cells with an oval nucleus having a prominent nucleolus. The cells are like absorptive cells or immature cells of the small intestine. Similarly to the biopsy specimen, the nucleus is located along the basement membrane, but goblet cells are decreased in number. Since there is no tendency of the cells to differentiate from the bottom toward the surface of the glands, very well-differentiated tubular carcinoma, noninvasive, is diagnosed. The lesion was completely resected.

Case 5, IIc

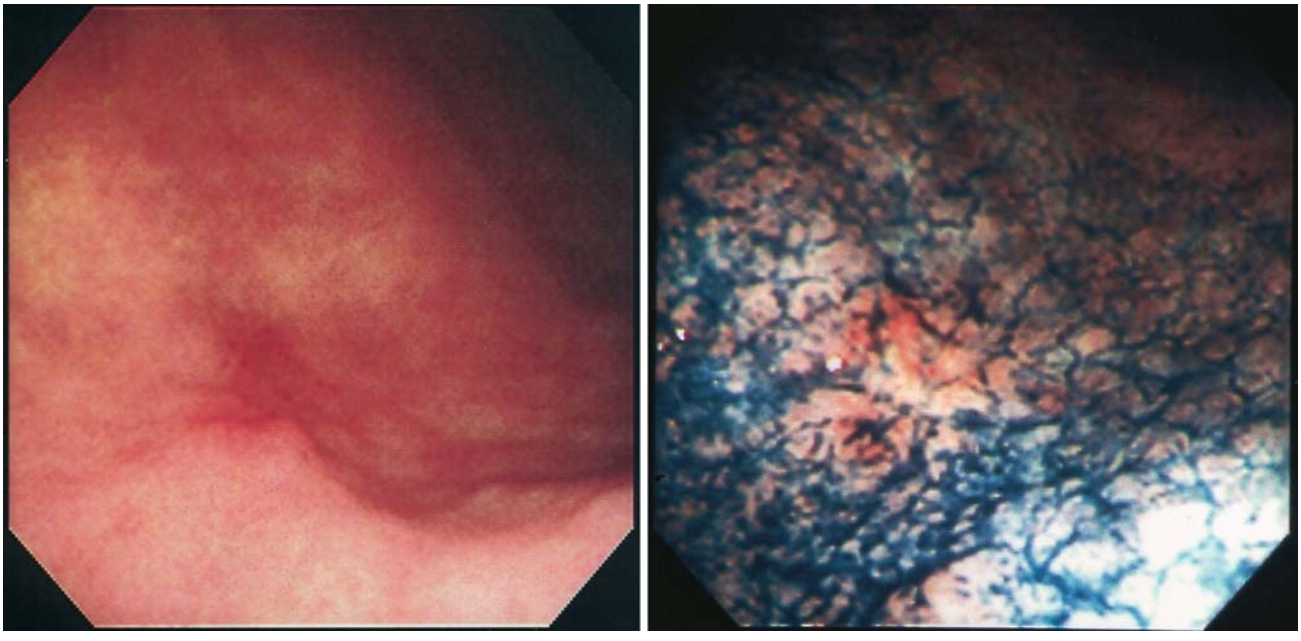


Fig. 5. **A** Antrum, greater curvature. **B** Same site after spraying indigo carmine

Table 5. Gastric lesion 5

Biopsy: × / Resection: ○	W W	W W	W	W W	W W	W W	W W	W W	J	W W	W J	W J J	J J W J J	W J J J
Regenerative changes	×													
Indefinite for neoplasia		×												
Adenoma/dysplasia														
low-grade			×	×										
high-grade					⊗	×								
Carcinoma														
suspected						○	⊗	×		×				
non-invasive			○						×				×	
intramucosal	○	○						○	○		⊗			×
submucosal				○						○		○	○	

Case Description

A man, aged 67 years, with a history of recurrent gastric ulcers and ischemic heart disease, underwent upper GI screening by endoscopic examination. Apart from two gastric ulcer scars, a lesion of 7 mm in diameter at the greater curvature of the antrum and a lesion of about 15 mm in diameter at the greater curvature of the corpus were found and biopsied. Four months later endoscopic ultrasonographic examination and endoscopic resection of both lesions were performed. Histological examination revealed submucosal invasion of one of the lesions. Moreover, the resection margins were not free of tumor. Three months later subtotal gastrectomy with lymph node resection was performed. In the surgical specimen, no neoplastic changes could be observed.

Endoscopy Commentary

Anthony T.R. Axon (UK)[1]

History

It is possible that a man of 67 years with a history of recurrent gastric ulcer would have been referred for upper digestive endoscopy in the West, particularly if he was complaining of gastric symptoms.

Endoscopic Appearance

The gastric antrum shows some slight erythema and irregularity on the greater curve. There is, however, no evidence of ulceration, neither does the antrum appear atrophic nor contain intestinal metaplasia macroscopically.

Dye spraying shows slight abnormality in the areae gastricae. Dye spraying would not have been undertaken in the West in this case and had it been done, it is unlikely that it would have raised suspicion. Western endoscopists do biopsy areas of irregularity so it is possible that a biopsy might have been taken from the affected area, but in view of the past history of gastric ulcer it is probable that the irregularity would have been attributed to scarring from the previous ulcers. On balance, I think most endoscopists would probably not have specifically biopsied that area.

A Western endoscopist looking at this lesion would regard it as irregular but flat, and I think would describe it more as IIb than IIc if making an assessment; however, as indicated earlier, we have little experience of these lesions in the West.

Histology

Had biopsies been taken the Western pathologists would have rated the appearance as high grade or worse. As indicated earlier, the high-grade dysplasia would probably have led to further endoscopies and more biopsies and that would have confirmed a presence of high-grade dysplasia or worse. A diagnosis of indefinite for neoplasia would also have led to further endoscopic examination.

Management

The presence of high-grade dysplasia or cancer will undoubtedly have led to surgical referral and gastric resection, in this case probably partial gastrectomy.

Summary

It is possible that this patient would have been referred for endoscopy in the West, but I do not believe that the endoscopist would have diagnosed or been suspicious of cancer at endoscopy. It is possible that biopsies would have been taken from the affected area, in which case the patient would have been referred for gastric resection.

Endoscopy Commentary

Shigeaki Yoshida (Japan)

A shallow, depressed lesion can be pointed out on the greater curvature of the antrum. In conventional endoscopy (Fig. 5A), its finding is described as “faint and monotonous hyperemic appearance of which the margin is unclear.” Since this is one of the representative findings in gastritis-like early cancer [1, 2], the malignancy of the lesion is highly suggestive.

The question is how to estimate the lateral extent of cancerous invasion. Actually, it is hard to trace the definite margin of the hyperemic area in the conventional endoscopic picture, but precise observation clarifies that there are two components in this area. One is the slightly elevated formation with shallow depression on the oral side and the other the shallow depression on the faint fold-like structure on the anal side. Hence, whether or not the invasion includes both components appears to be a point that needs clarifying, and a dye-spraying picture (Fig. 5B) reveals nonspecific mucosa dividing the above two components, indicating the possibility of two different lesions or the possibility that a biopsy was taken from the center of a single antral lesion. Although details are not well visualized, the

[1]See footnote on p. 4.

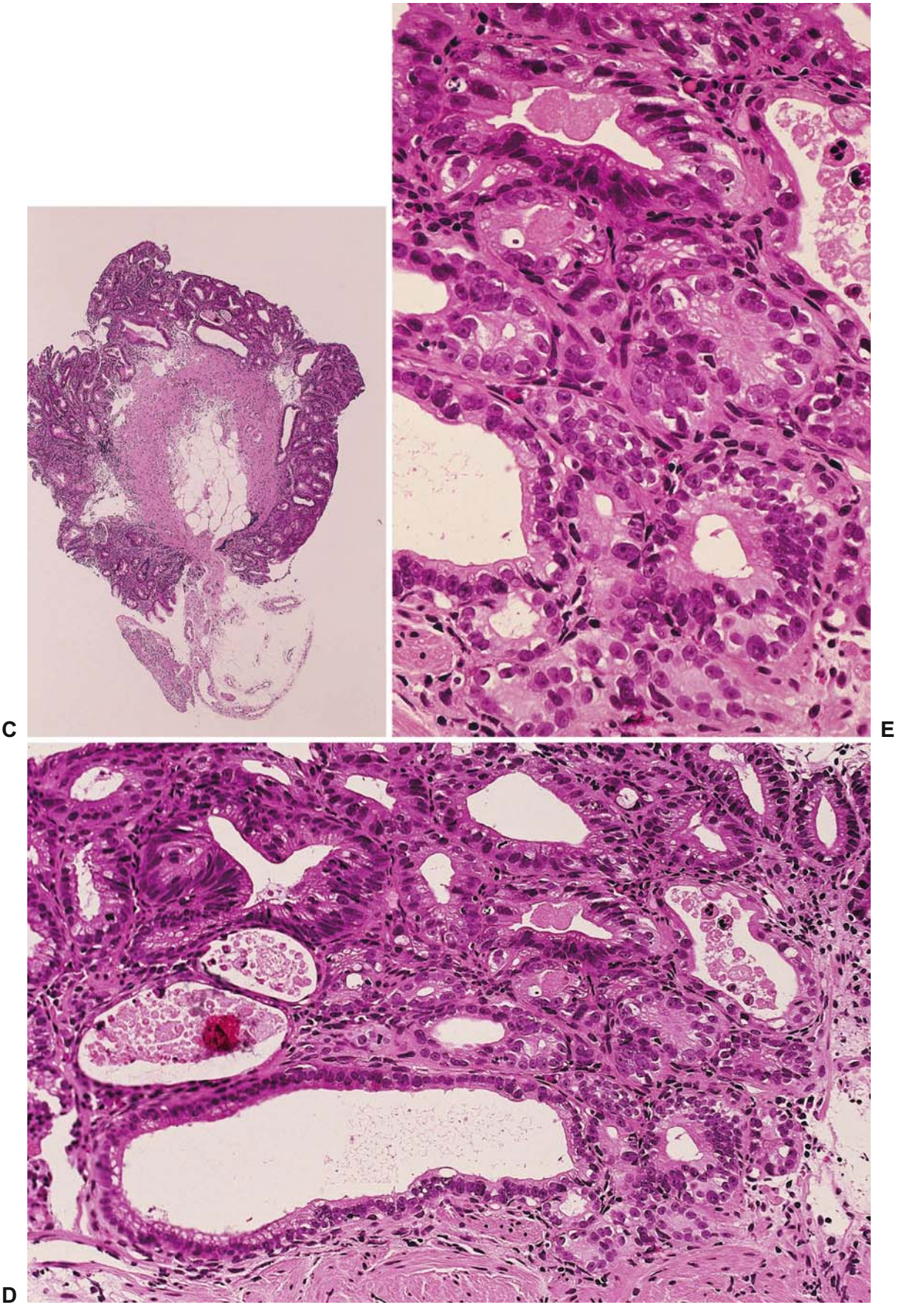


Fig. 5. **C** Biopsy specimen. **D** Detail of **C**. **E** Detail of **D**

invasive area of IIc can be estimated as limited to within the depressed area on the oral side, due to its well-demarcated marginal irregularity. Malignancy is also highly suggested in the shallow depressed area on the anal side, due to a hyperemic area whose margin is partially irregular, and a tiny star-shaped depression located at the edge of the anterior wall of this area. If the invasion includes both anal and oral areas, the size is estimated as 10–12 mm, referring to the diameter of *areae gastricae*. Otherwise, if they were separated, the oral lesion may be less than 5 mm and the anal one 8–10 mm in size, respectively.

As to the histological type, it can be said that cancerous lesions in the antrum showing a faint and monotonous hyperemic appearance are mostly of the differentiated type histologically. In the case presented here there is no finding suggesting submucosal invasion or ulcerative change within the cancerous area.

Endoscopically, therefore, the final diagnosis of this case should be two areas of nonulcerative IIc, being of the differentiated type histologically, whose sizes are estimated as less than 5 mm orally and 8–10 mm anally, respectively.

Endoscopic mucosal resection can be indicated because there is no suggestive finding of submucosal invasion.

References

1. Yoshida S, Yamaguchi H, Saito D et al (1993) Endoscopic diagnosis; latest trends. In: Nishi M, Ichikawa H, Nakajima T, et al (eds) Gastric cancer Springer, Tokyo, pp 246–262
2. Yoshida S (1998) Endoscipic diagnosis and treatment of early cancer in the alimentary tract. Digestion 59:502–508

Pathology Commentary

Manfred Stolte (Germany)

It can already be seen in the low-power overview (Fig. 5C) that the normal glands of the gastric mucosa have been replaced by a highly irregular arrangement of neoplastic tubuli. Under higher magnification (Fig. 5D and E), the tubuli that are lined by neoplastic epithelial cells are unusually densely packed and show some irregular branching of varying caliber. This finding is incompatible with the diagnosis of intraepithelial neoplasia (dysplasia). Rather, there is almost complete replacement of the original lamina propria, now hardly recognizable, by invasive neoplastic structures. In Fig. 5E, tubular formations are focally unrecognizable. In addition, the usual cytological criteria for the diagnosis of carcinoma are met.

In the overview of the endoscopic mucosectomy specimen (Fig. 5F) it is already clear that the neoplasm is not limited to the mucosa, but that irregularly branched neoplastic tubuli of varying caliber have penetrated through the muscularis mucosae and extend into the upper part of the submucosa. Under higher magnification (Fig. 5G) it becomes clear that this cannot be a pseudoinvasion, since there is no destruction of the muscularis mucosae, no fibrosis of the adjacent lamina propria, and no other evidence of a prior traumatic lesion of the mucosa and submucosa with secondary displacement of glandular components into the submucosa. In the high power views of the invasive part of the tumor in the submucosa (Fig. 5G and I), the changes in the cell nuclei and their position are not as marked as in the biopsy material. Here, many of the nuclei are located in the base of the cylindrical epithelial cells, are only mildly enlarged, and are moderately hyperchromatic. Prominent nucleoli are also seen less frequently. The lightly stained cytoplasm indicates that mucus is still being produced. These histological and cytological criteria strongly favor an adenocarcinoma with gastric differentiation, which might be confirmed by immunohistochemistry for MUC6.

In conclusion, therefore, both the biopsy and the endoscopic mucosectomy specimens reveal a well-differentiated adenocarcinoma. In the mucosectomy specimen, there is already focal invasion of the carcinoma into the upper part of the submucosa (sm1) but without invasion of lymphatic or blood vessels. The histological structure and the cytology of the tumor cells in this case indicate an adenocarcinoma with gastric differentiation.

An analysis of the diagnoses again reveals considerable variability. Nine Western pathologists diagnosed no carcinoma in the biopsy, but corrected their diagnosis in the mucosectomy specimen. However, only two of these pathologists interpreted the neoplastic glands in the submucosa as invasive submucosal carcinoma, while the majority of the Japanese pathologists and four Western pathologists who adopt the "Japanese viewpoint" interpreted the findings as clearly showing a submucosal carcinoma.

Pathology Commentary

Yo Kato (Japan)

The biopsy specimen is compacted with slightly irregular-shaped and -sized round glands, particularly in the upper half of the mucosa (Fig. 5C). In the upper part of Fig. 5D, medium-sized glands with occasional amorphous excretion or cell debris are composed of

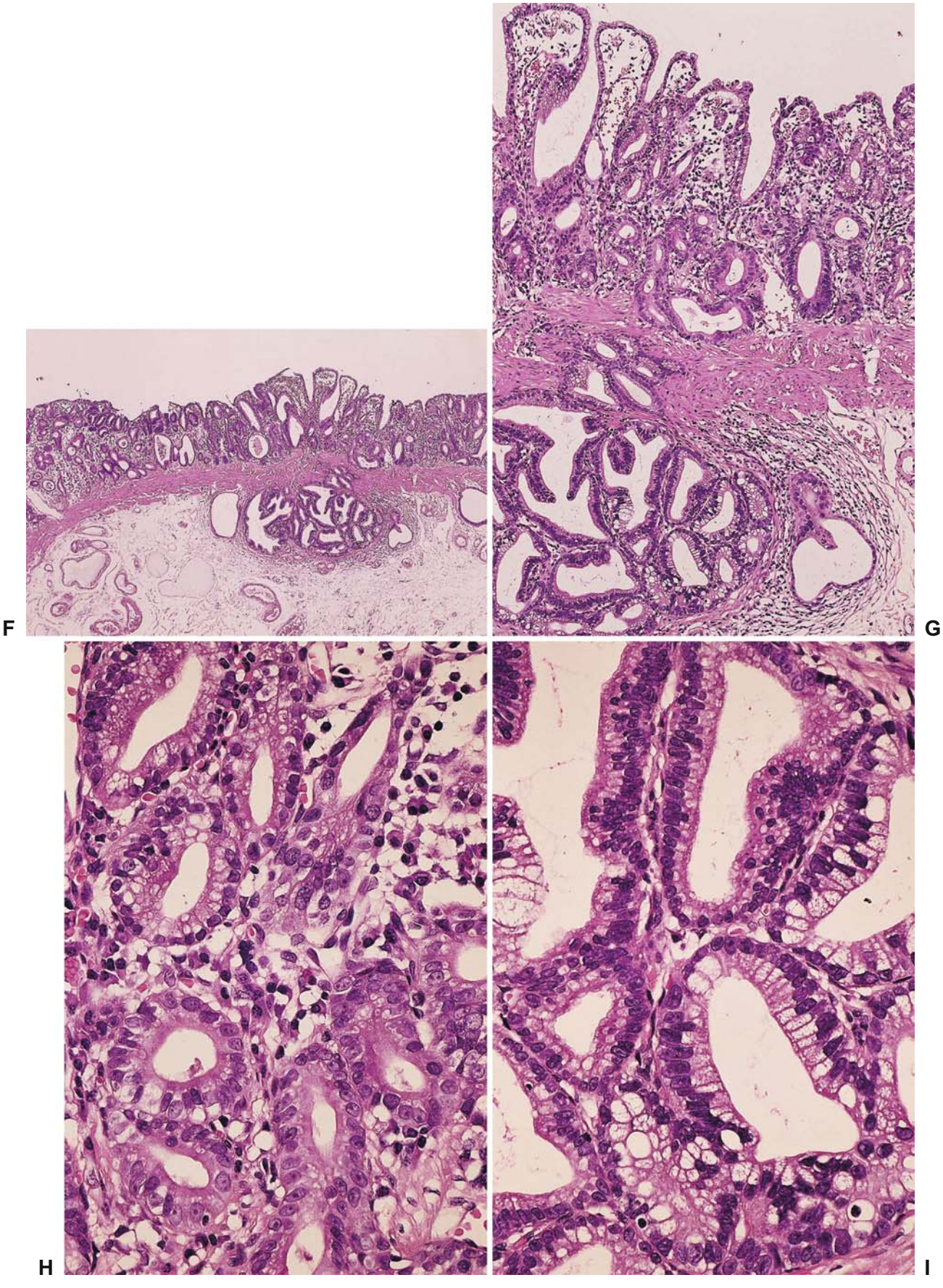


Fig. 5. **F** Resected specimen. **G** Detail of **F**. **H** Detail of **G** (mucosal portion). **I** Detail of **G** (submucosal portion)

eosinophilic columnar to cuboidal cells, i.e., intestinal-type cells, with an ovoid or spindle-shaped hyperchromatic nucleus. Here there is loss of polarity of the nuclei, and thus stratification of the nuclei is rather prominent. On the other hand, in the middle to lower part of the figure, small and large glands and a cystic-dilated gland are mixed up, and their constituent of light eosinophilic cuboidal cells is of immature gastric or pyloric gland phenotype, equally equipped with a swollen, round, pale nucleus and a prominent nucleolus. With these findings of the biopsy specimen, the atypical glands are diagnosed simply as very well-differentiated carcinoma without referring to "invasive or noninvasive" according to Japanese criteria, but will be interpreted as high-grade dysplasia/neoplasia from the Western viewpoint since there are no evident findings of invasion. Some small glands in the lower part of the figure and some parts of cystic-dilated glands, however, can be residues of non-neoplastic glands or epithelium since the nuclear sizes are smaller than those in the glands of the middle part (Fig. 5D,E). Concerning the epithelial phenotype, a mixed intestinal and gastric one is considered.

The EMR specimen shows both mucosal and submucosal lesions, consisting of slightly irregular-shaped tubular glands, and the atypical glands clearly invade the submucosa through the muscularis mucosae (Fig. 5F,G). The high-power view of the mucosal lesion as shown in Fig. 5H is more homogeneous in pattern than in the biopsy specimen (Fig. 5E), formed by round tubular glands made of cuboidal cells with a round nucleus and a prominent nucleolus. Figure 5I is a high-power view of the submucosal lesion, showing aggregates of slightly irregular-shaped glands composed of cuboidal mucinous cells with a hyperchromatic round to oval nucleus. These mucinous cells appear partly pyloric gland-like, partly goblet cell-like. It should be made clear that similar atypical glands have already appeared in the mucosa where the invasive pattern is not clear. As a whole, the lesion is diagnosed as very well-differentiated carcinoma with submucosal invasion.

Case 6, IIa

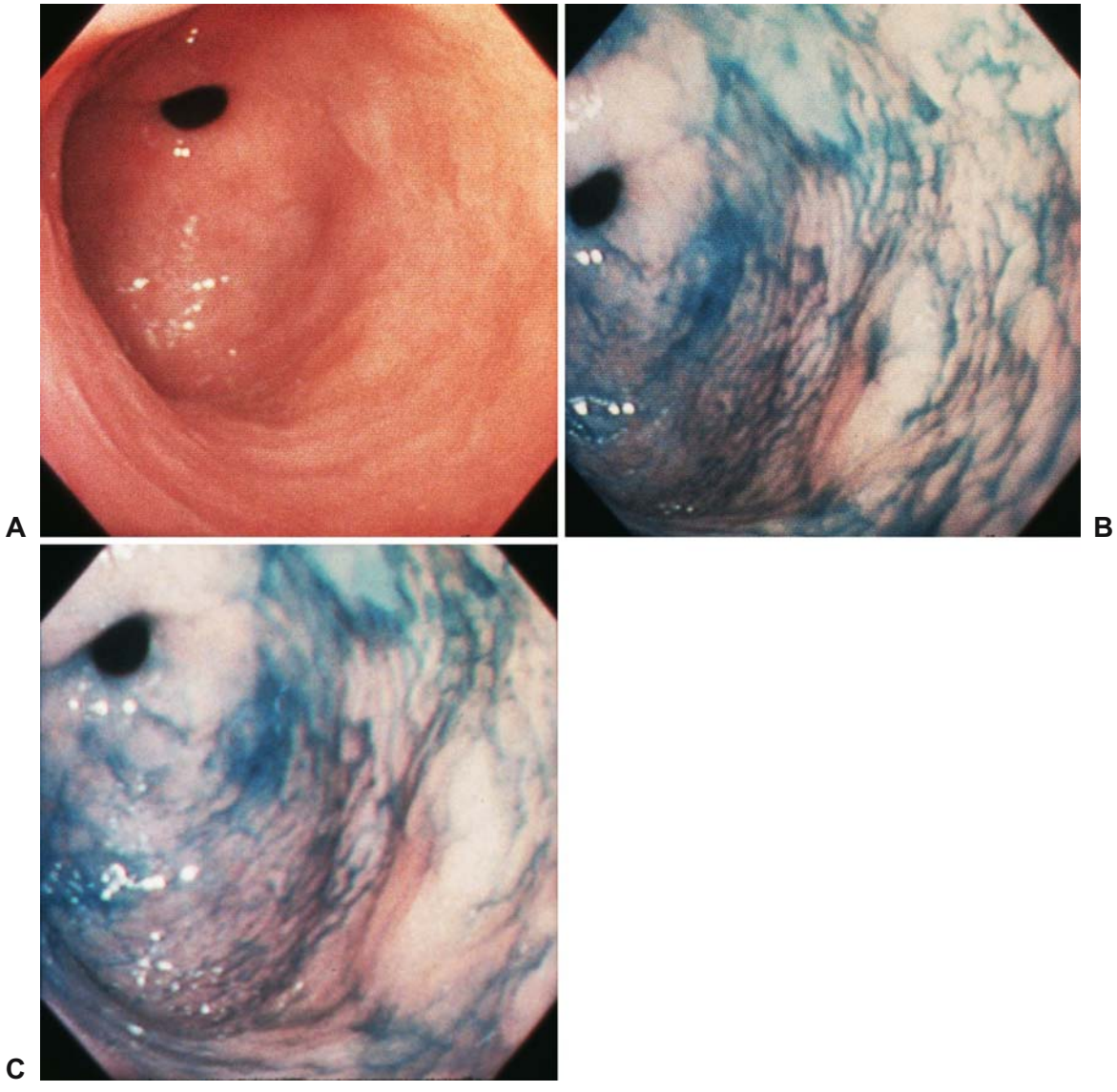


Fig. 6. **A** Antrum, posterior wall. **B** Same site after spraying indigo carmine. **C** Close-up view

Table 6. Gastric lesion 6

Biopsy: × / Resection: ○	W WW W WW WJ	WW WJ WW WW WJ	W W	W J	J	W	J	J	J	J J J
Adenoma/dysplasia										
low-grade	⊗	○	○	○						
high-grade		×			○	○	×			
Carcinoma										
suspected			×					⊗	○	
non-invasive				×	×		○		×	⊗
intramucosal						×				

Case Description

A man, aged 69 years, known to have von Recklinghausen disease and Parkinson syndrome, underwent upper GI screening by endoscopic examination. A lesion of about 1 cm in diameter was found at the posterior wall of the antrum and was biopsied. Two months later he underwent endoscopic ultrasonographic examination and shortly thereafter, endoscopic resection was performed. The resection margins were free of tumor.

Endoscopy Commentary

Anthony T.R. Axon (UK)[1]

History

This case again is one that was referred for upper GI cancer screening and would not have occurred in the West. Endoscopy in the West is carried out only for symptoms, and Western endoscopists therefore seek a cause of the symptoms of which the patient is complaining, looking for ulcers in the duodenum or stomach, evidence of reflux esophagitis, gastric stasis, erosions, and gastritis. They do not look for slight irregularities or changes in color because these are not appearances that give rise to symptoms. This means that Western endoscopists miss these early changes of cancer. It is this difference of approach that influences the endoscopist in that you tend to "find what you are looking for." The Japanese, on the other hand, with a high incidence of cancer, search for these early cancers and find them.

Endoscopic Appearance

In this case the appearance of the antrum to a Western endoscopist appears to be normal. Dye spray, however, reveals a slightly elevated lesion on the posterior wall of the antrum with a depression in its center. As shown on the dye spray the appearance is suspicious of cancer and if this was identified by a Western endoscopist, biopsies would have been taken.

Histology

It is interesting that the Western pathologists felt that the appearance was that of low-grade, or at worst, high-grade dysplasia. A report of this nature would have led to a further endoscopy with more biopsies; the patient would then have been put into a surveillance routine that would have caused the pathologists to take a second opinion. In time, if high-grade dysplasia was again identified the patient would have been referred for gastric resection.

Summary

Again, this is a case where the patient would not have been submitted for endoscopy in the West and where the lesion would have been missed. Had it been identified, further endoscopies with biopsy would have been undertaken and eventually it is likely that it would have led to gastrectomy.

Endoscopy Commentary

Shigeaki Yoshida (Japan)

On the posterior wall of the antrum five or more superficial elevated lesions having a shallow central depression can be pointed out on conventional endoscopy (Fig. 6A). They are similar to each other in their gross appearance, though the most proximal lesion is larger than any of the other lesions. Because these elevated lesions show nonspecific color change and no irregularity in the depressed component, they are diagnosed as erosive gastritis in this picture. Further examination using dye-spraying endoscopy is required to make the differential diagnosis more accurate in this type of lesion.

A dye-spraying picture (Fig. 6B) reveals that only the most proximal lesion is actually solid, though the others have changed their appearance to be inconspicuous and nonspecific. In that lesion, elevated components are shown to be discolored and lustrous like gastric adenomas, but a faint hyperemic appearance in the shallow depression seen particularly in the close-up view is strongly suggestive of its malignancy (Fig. 6C).

According to the gross appearance of a plateau-like elevation involving a negligible shallow depression, the lesion can be diagnosed as type IIa early cancer, whose size is estimated to be around 1 cm, because the circumference of the prepyloric region is usually around 8 cm in the resected specimen.

In type IIa early cancer deeper invasion is generally rare, and in such a case the lesion is usually larger than 2 cm and frequently incorporates an eroded shallow depression. In addition, the undifferentiated type is rare in type IIa early cancer, and in such a case the lesion shows an eroded surface structure and/or discoloration without lustrous appearance. Hence, the lesion presented here can be estimated as mucosal cancer of the differentiated type, and EMR should be the first choice for the treatment of this lesion because of its size, histological type, and estimated depth of invasion.

[1]See footnote on p. 4.

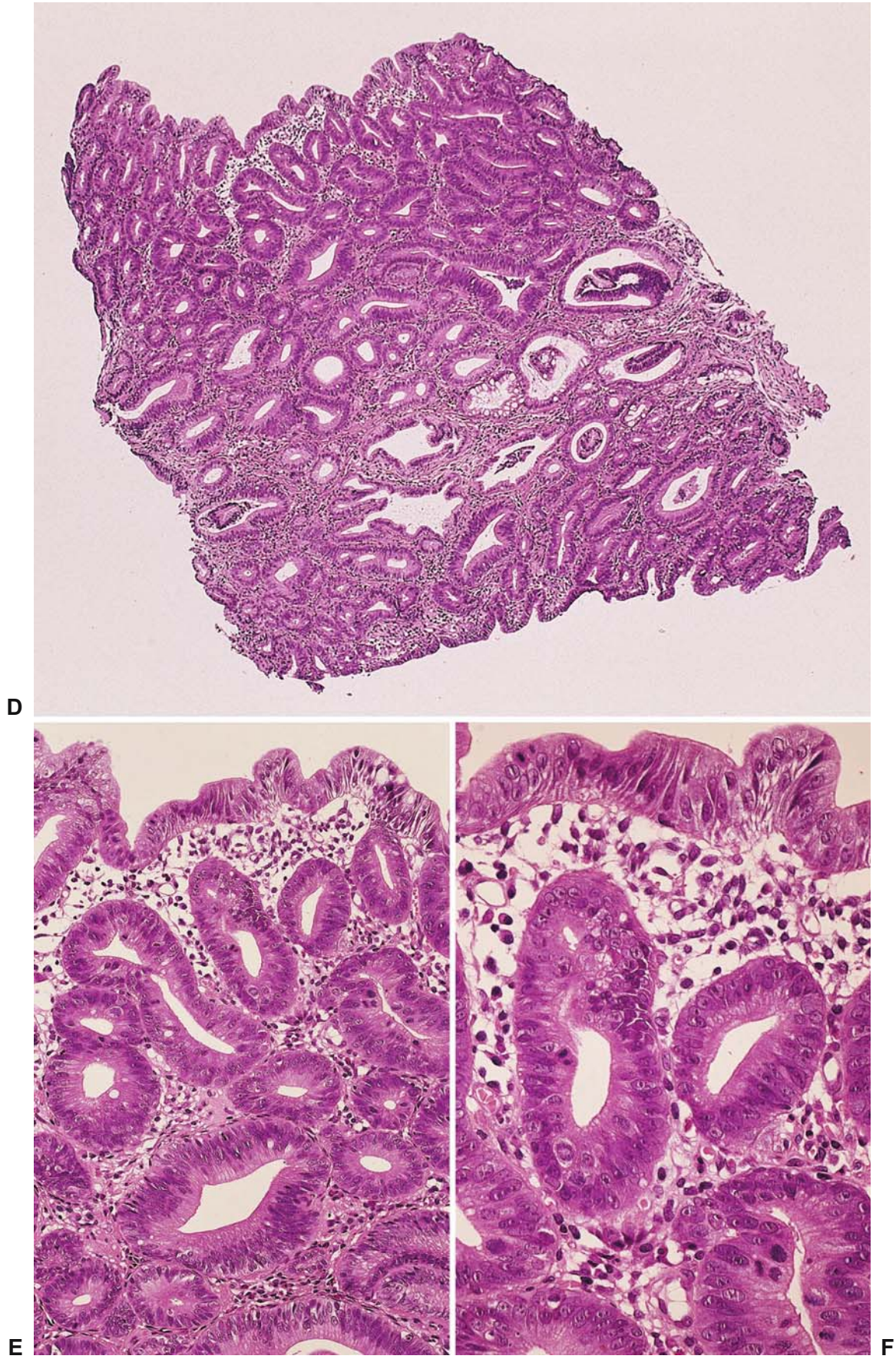
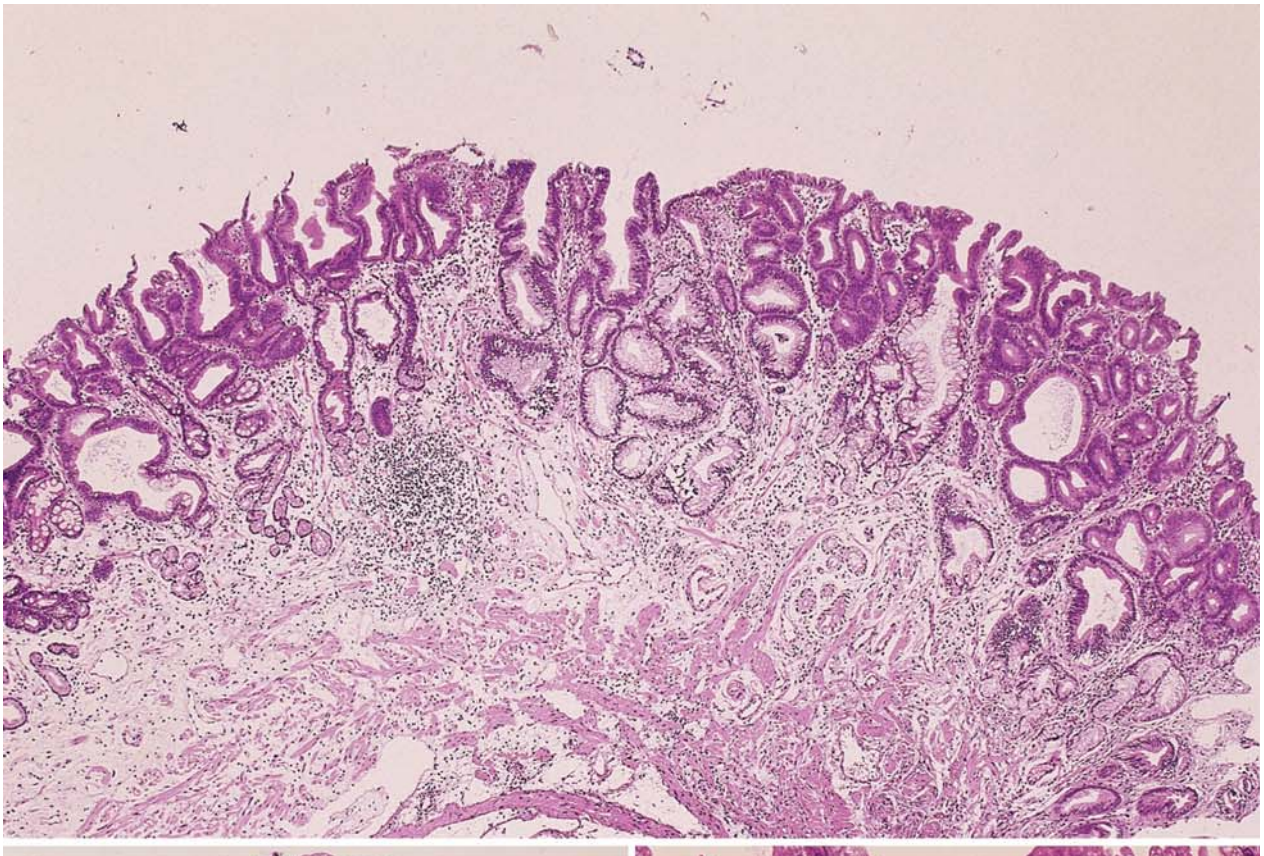
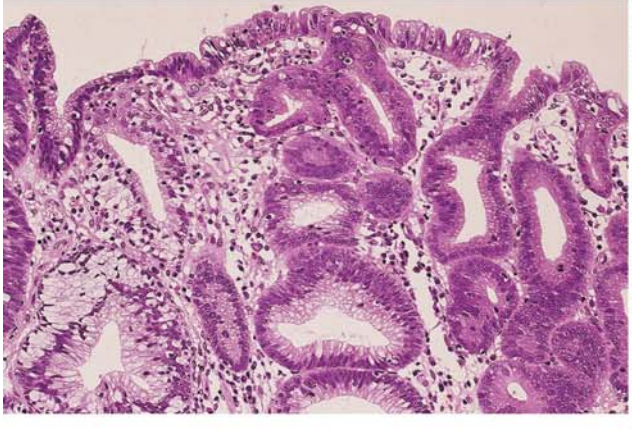


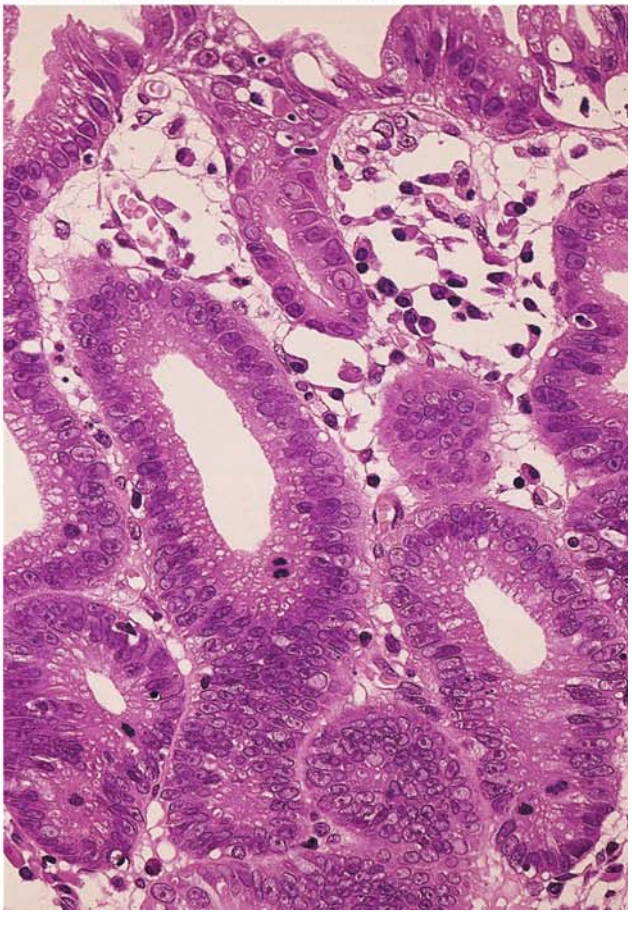
Fig. 6. **D** Biopsy specimen. **E** Detail of **D**. **F** Detail of **E**



G



H



I

Fig. 6. **G** Resected specimen. **H** Detail of **G**. **I** Detail of **H**

Pathology Commentary

Manfred Stolte (Germany)

The endoscopic appearance (Fig. 6A–C) already shows that the lesion is neoplastic. In light of the endoscopic findings, the histological differential diagnosis of the biopsy specimen was concerned with determining whether the lesion is only an adenoma or a type IIa early gastric carcinoma. The central depression of the elevated lesion is a hint that this is a carcinoma.

The neoplastic nature of the lesion is confirmed in the biopsy material. In higher magnification (Fig. 6E and F), the architecture of the neoplastic tubuli is still relatively ordered, so that the differential diagnosis has to be made between high-grade dysplasia and noninvasive carcinoma. The cytological changes of the tumor cells with their irregular arrangement of nuclei, irregular chromatin, prominent nucleoli, and multiple pathological mitotic figures are incompatible with the diagnosis of low-grade dysplasia.

In the low-power view of the biopsy specimen (Fig. 6D), the architecture of the neoplastic glands is also incompatible with an adenoma. In addition, it also reveals irregular branches and foci of horizontal neoplastic tubuli, suspicious for transition to invasive intramucosal carcinoma.

In the endoscopic mucosectomy specimen, this suspicion would appear to be validated (Fig. 6G), since here we find a mainly parallel expansion of neoplastic tubuli in the upper third of the mucosa, a finding which is incompatible with an adenoma.

Under higher magnification (Fig. 6H and I), the nuclear changes already described in the biopsy material show that the findings go beyond low-grade dysplasia. Furthermore, foci of irregularly arranged neoplastic tubuli of varying caliber are to be seen, which in my view indicate initial invasive growth.

In conclusion, therefore, I would diagnose a well-differentiated invasive intramucosal adenocarcinoma.

The variability in the diagnoses of this difficult "borderline case" is understandable. This applies, however, only to the differentiation between high-grade dysplasia, noninvasive carcinoma, and intramucosal carcinoma. The diagnosis of low-grade dysplasia made by many, mainly Western, pathologists is definitely an "underdiagnosis."

Pathology Commentary

Yo Kato (Japan)

The biopsy specimen is, though tangentially cut, filled with many rather equal-shaped and -sized atypical tubular or round glands except for the center which contains an aggregate of non-neoplastic glands (Fig. 6D). The glands consist of eosinophilic columnar cells, appearing to be of immature intestinal type, with a round or oval plump nucleus, with a conspicuous nucleolus throughout the glands. Mitoses are also prominent. Since the tendency of the cells to differentiate from the bottom toward the surface of the lesion is not definite, both adenoma with severe atypia (i.e., high-grade adenoma) and very well-differentiated tubular carcinoma (i.e., noninvasive carcinoma) are listed in the differential diagnosis (Fig. 6E). Although the nucleus is situated along the basement membrane, with the findings described above and too conspicuously swollen nuclei as shown in Fig. 6F, I interpreted the lesion as the latter of the two mentioned above (Fig. 6F). This is partly because we pathologists, in general, do not like to make an underdiagnosis at the time of biopsy.

In the EMR specimen (Fig. 6G), the lesion is situated in the upper half of the mucosa, consisting, similarly to the biopsy specimen (Fig. 6D), of rather equal-shaped and -sized atypical tubular or round glands. Again, since no maturation tendency throughout the epithelium with generally round, plump nuclei exists, with no further evidence of invasion, I consider the lesion as noninvasive adenocarcinoma of very well-differentiated type (Fig. 6H,I). The constituent tumor cells look like the gastric or intestinal phenotype because of the presence of small mucus droplets in the cytoplasm of the tumor cells (Fig. 6H,I). Interestingly, there is a double-layered gland with many goblet cells in the figures (Fig. 6G, center and Fig. 6H, left): the gland seems to be non-neoplastic, but its significance is unknown.

Case 7, IIa

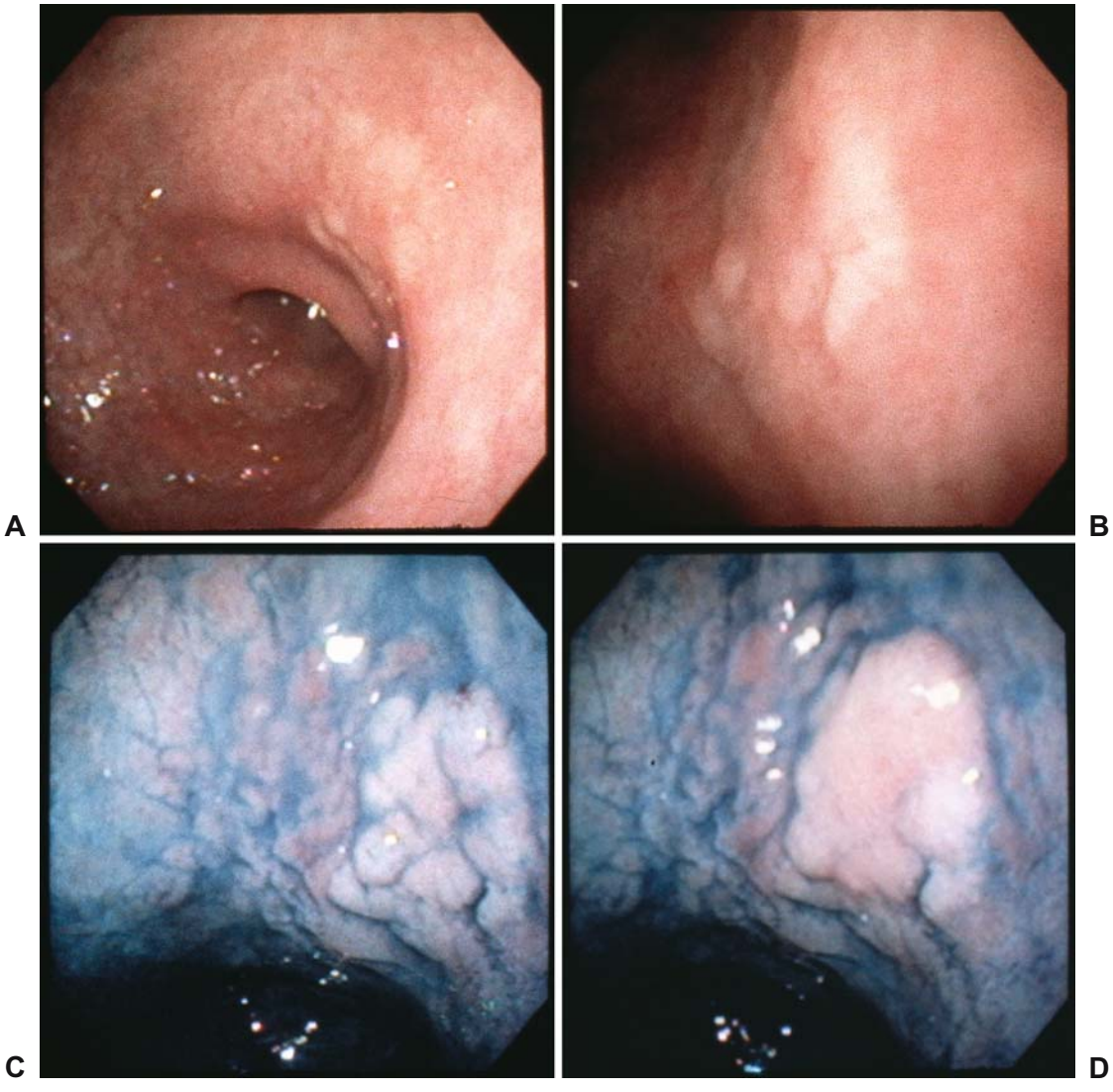


Fig. 7. **A** Angulus, lesser curvature. **B** Close-up view. **C** Same site immediately after spraying indigo carmine. **D** Same site a short while after spraying indigo carmine

Table 7. Gastric lesion 7

Biopsy: × Resection: ○	W W J	W W W	W	W W W J	W W J	J	J	W	W	W	W W J	J J J
Adenoma/dysplasia												
low-grade	⊗	×	○		×							
high-grade		○		⊗		○	×	○	×			
Carcinoma												
suspected			×			×	○				×	
non-invasive					○						○	⊗
intramucosal								×	○			

Case Description

A man, aged 63 years, with chronic hepatitis B and esophageal varices, regularly underwent upper GI endoscopic examinations. At the posterior wall side of the lesser curvature of the angulus a lesion was found. From a biopsy adenoma was diagnosed and it was followed up. Two years later the lesion had changed in shape. It measured 14 mm in diameter. Three weeks later endoscopic ultrasonographic examination and endoscopic resection were performed. The resection margins were free of tumor. On follow-up endoscopic examinations, no local recurrence was found.

Endoscopy Commentary

Anthony T.R. Axon (UK)[1]

History

This case is one where regular endoscopic examination would have been performed in the West in order to keep a check on the esophageal varices. Western endoscopists do examine the stomach and duodenum as a routine when checking for varices, and it is possible that the lesion on the lesser curve would have been identified. It has a plaque-like appearance that is irregular, with a color change. The appearances are distinctly unusual and not suggestive of a portal gastropathy. Although dye spray would not have been used in the West, I believe that biopsies would have been taken from this lesion.

Histology

Most of the Western pathologists diagnose either low-grade or high-grade dysplasia, and this would have led to further examinations and biopsy. A diagnosis of high-grade dysplasia would eventually have been made.

Endoscopic Appearance

Endoscopically, the flat nature of the lesion with protuberant areas would have probably been called type IIa or b in that there is no evidence of depression in the lesion and, although the patient does have significant other problems, undoubtedly a surgical opinion would have been sought.

Management

The presence of a lesion with high-grade dysplasia with these macroscopic changes would, I think, have led to surgical referral and to some form of gastric resection, but the portal hypertension and esophageal varices would have given cause for concern, and local therapy, if available, might have been considered.

I note from the history that a diagnosis of adenoma was made at an earlier stage. This is recognized to be a premalignant condition in the West, and further examinations with biopsy would have been undertaken.

Summary

This case describes a patient in whom the lesion would probably have been detected in the West. The combination of a macroscopic lesion with high-grade dysplasia would probably have led to surgical resection.

Endoscopy Commentary

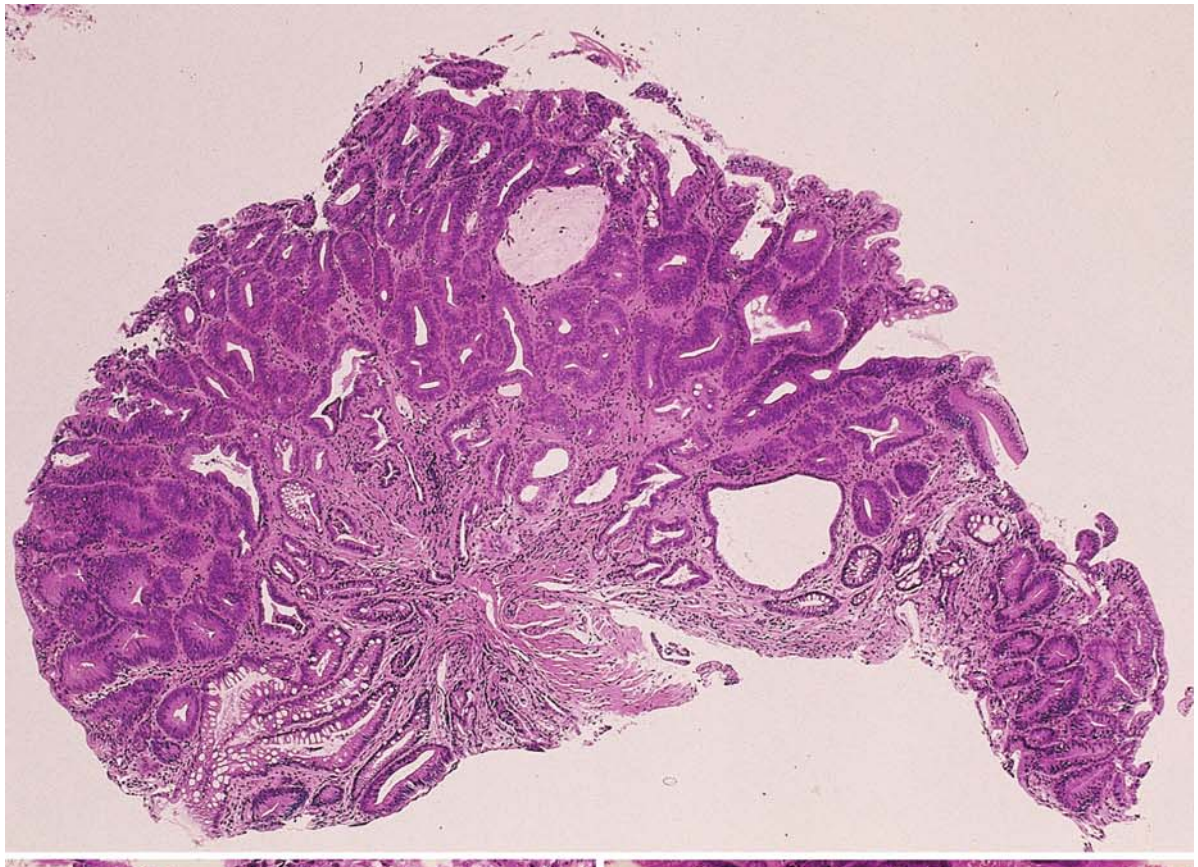
Shigeaki Yoshida (Japan)

A whitish, elevated lesion is located on the lesser curvature of the angulus. A slightly hyperemic appearance is detectable from the center to the anal side of the lesion on conventional endoscopy (Fig. 7A and B). According to the whitish (discolored) nodular elevation indicating the possibility of adenoma and the hyperemic appearance indicating that of carcinoma, a cancerous lesion with adenoma would be a tentative diagnosis from conventional endoscopy.

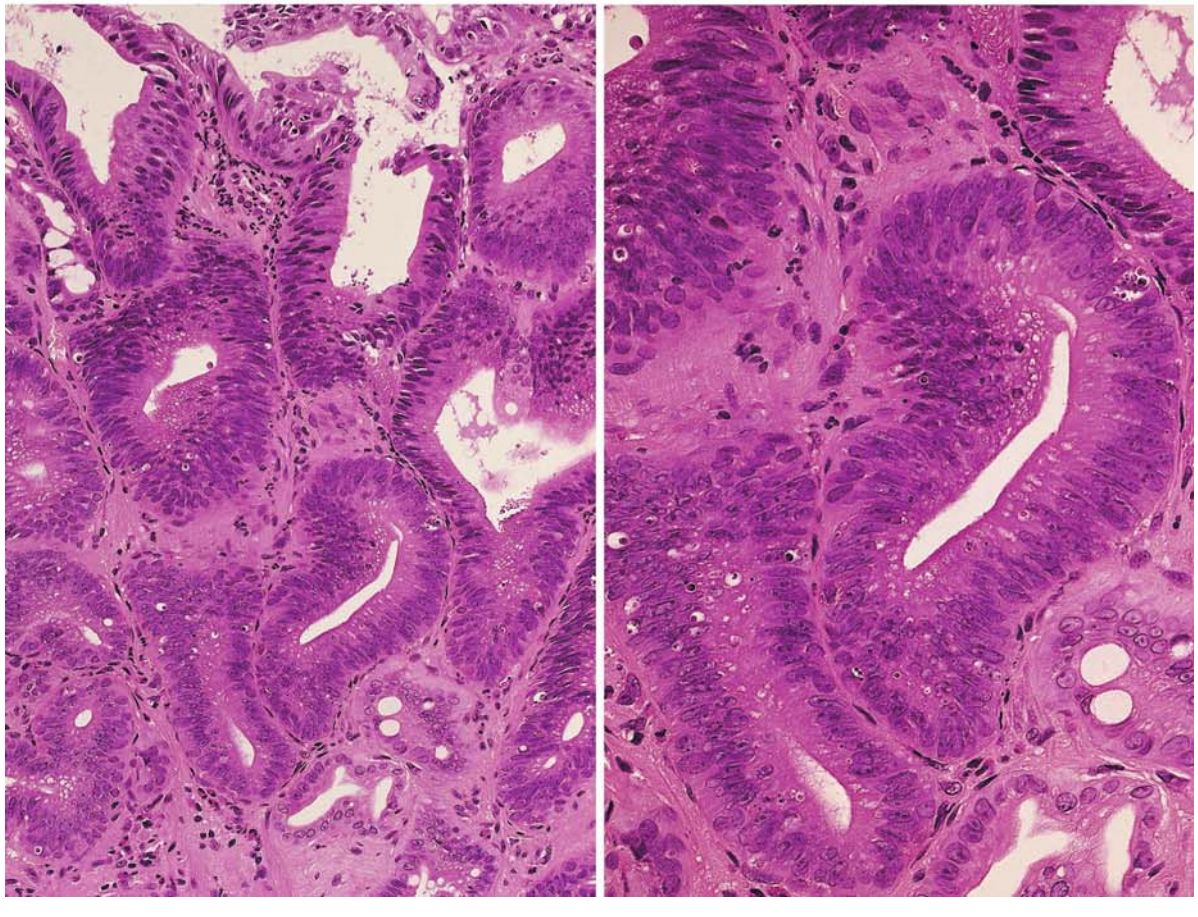
A dye-spraying endoscopy picture (Fig. 7C) clarifies the construction of this elevated lesion in detail, i.e., a gathering of small nodules. The slightly hyperemic appearance noted on conventional endoscopy becomes inconspicuous in this picture. This may indicate a high probability of adenoma, rather than carcinoma, though the surface of the elevated components is not lustrous as in the typical appearance of an adenoma. In contrast, another picture (Fig. 7D) showing a close-up view of the lesion reveals hyperemic surface mucosa, indicating malignancy. Nevertheless, this picture is not suitable for making a definite diagnosis due to poor imaging caused by too much catchlight.

From the above, gastric adenoma rather than carcinoma should be the final endoscopic diagnosis. Considering that during the clinical course this lesion changed in shape, however, the diagnosis of carcinoma appears to be more likely than that of adenoma. In such a case it is difficult to make a definite endoscopic diagnosis; differentiation of carcinoma from adenoma is occasionally difficult even when assessing histological material obtained by biopsy. Endoscopic mucosal resection should be recommended to reach a definite histological diagnosis on such an occasion.

[1]See footnote on p. 4.

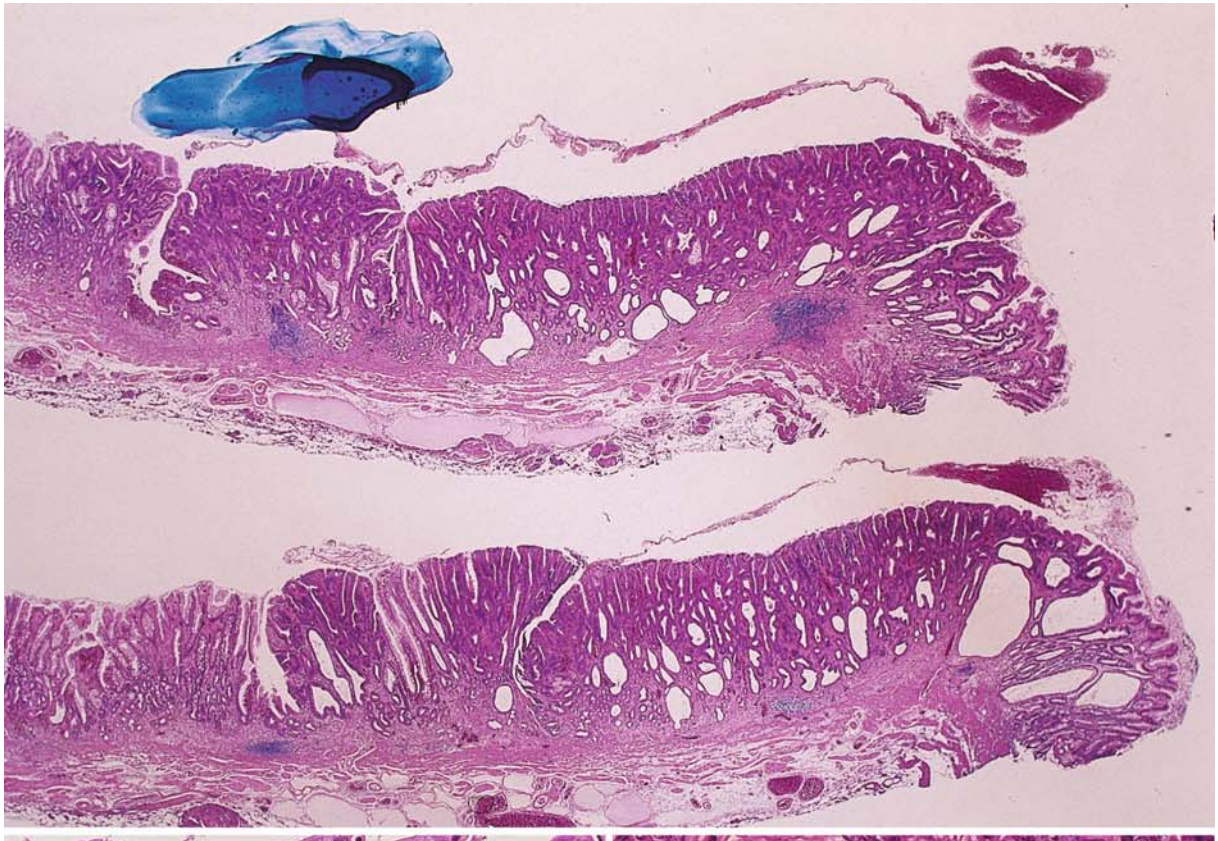


E

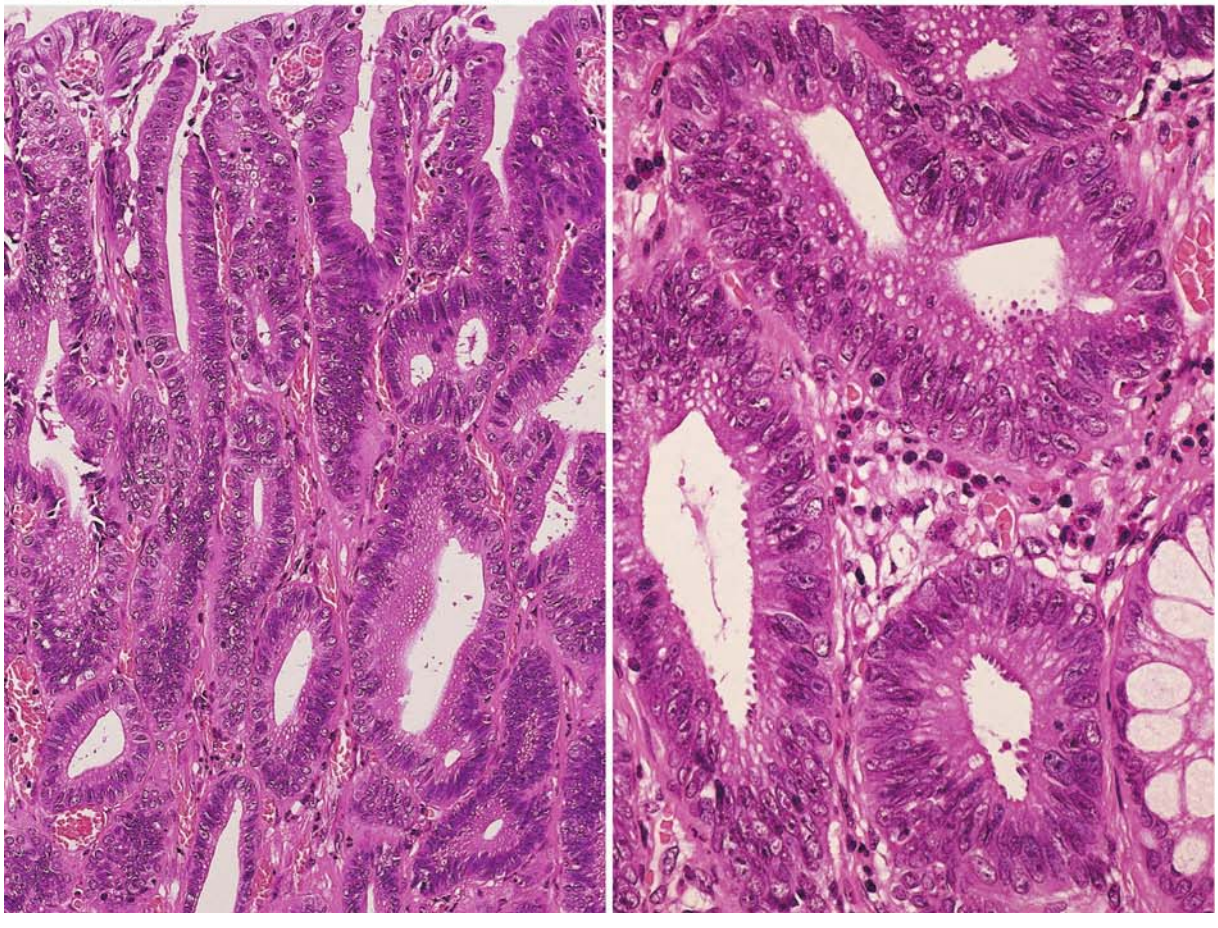


F G

Fig. 7. **E** Biopsy specimen. **F** Detail of **E**. **G** Detail of **F**



H



I J

Fig. 7. **H** Resected specimen. **I** Detail of **H**. **J** Detail of **H**

The size of the lesion is estimated as less than 2 cm, because the arch of the gastric angle is estimated to be 6 cm long, i.e., half the circumference of the angular region, which corresponds to 6 cm away from the pylorus along the lesser curvature of the resected specimen. Also, an accessory lesion of a benign peptic ulcer scar may be located on the anterior wall side of the lesion, referred to as deformity of the gastric angle.

Pathology Commentary

Manfred Stolte (Germany)

The endoscopic appearance alone shows that this lesion must be a neoplasm, and the differentiation to be made is between adenoma and carcinoma; the irregular borders at the margin, together with the tiny tumor nests, tend to suggest a carcinoma.

In the biopsy material the diagnosis of neoplasia is already quite clear at low power (Fig. 7E). Even at this low magnification, irregular architecture with lateral expansion of individual neoplastic tubuli can be recognized. These can also be seen focally in the center of the lesion. At higher magnification (Fig. 7F and G), the diagnosis of neoplasia is confirmed. In Fig. 7F, some of the nuclei are still located at the base and are only moderately hyperchromatic. The architecture of the neoplastic tubuli, however, already shows irregularity. In Fig. 7G it is clear that the differential diagnosis is between high-grade dysplasia and carcinoma, since here we can see obviously enlarged nuclei, prominent nucleoli, and irregular chromatin.

This is confirmed in the endoscopic mucosectomy specimen, in particular in Fig. 7I and J. In the low-power view (Fig. 7H) we find a number of areas of highly irregular neoplastic architecture, and this is confirmed in Fig. 7I. Despite the fact that neither individual tumor cells nor tumor cell nests are seen in the lamina propria, I would diagnose neoplastic glandular infiltration of the lamina propria.

In conclusion, this is a "borderline case" between a noninvasive carcinoma limited to the mucosa and an invasive intramucosal carcinoma. In my opinion, the architecture of this neoplasia is more likely to indicate an invasive well-differentiated carcinoma limited to the mucosa.

In this case, again, the discrepancies in the diagnoses of the various pathologists are considerable. The diagnosis of low-grade dysplasia made by three Western and two Japanese pathologists is, with certainty, an "underdiagnosis." The diagnostic variability between high-grade dysplasia, noninvasive carcinoma, and invasive intramucosal carcinoma in this case is understandable.

Pathology Commentary

Yo Kato (Japan)

The biopsy specimen shows atypical tubular glands rather equally distributed (with the same density of glands) in the upper half of the mucosa (Fig. 7E). The glands are mostly round or tubular, though slightly distorted in places. The high-power view (Fig. 7G) demonstrates that the glands are composed of intestinal-type columnar cells with a slightly hyperchromatic slender nucleus, and that most of the nuclei are situated along the basement membrane. The nucleolus is not so conspicuous. Since a tendency of the cells to differentiate from the bottom with a round nucleus toward the surface with a slender nucleus exists (Fig. 7F), the diagnosis group III "tubular adenoma, moderate atypia" will be given by most Japanese pathologists according to the group classification presented by the JRSGC: the change corresponds to what Japanese doctors have long called "ATP (abbreviation of atypical epithelium or atypical epithelial lesion)" or "IIa subtype (a superficial elevated lesion to be distinguished from adenocarcinoma of the same macroscopic type, IIa)," etc., but these days the lesion is recommended by the World Health Organization Tumor Classification to be called "tubular adenoma."

The EMR specimen demonstrates a similar pattern as in the biopsy specimen (Fig. 7H). The dilated glands found occasionally in the deeper part of the biopsy specimen (Fig. 7E) exist frequently in the lower half of the mucosa or beneath the atypical lesion (Fig. 7H), which is a finding rather common for "ATP" or tubular adenoma. The high-power view of a part of the lesion indicates glands with an equal-shaped and -sized slightly swollen nucleus. Compared with the biopsy specimen (Fig. 7F), the tendency of cell differentiation is not clear in the EMR specimen (Fig. 7I), but a faint tendency still seems to be kept in the right half of the picture as the cell nucleus becomes rather slender, with the cells reaching the surface of the lesion. Ischemic change, suggested by fibromuscular proliferation in the lamina propria mucosae, may modify the pattern typical for adenoma.