GASTROINTESTINAL PATHOLOGY SOCIETY

Sunday, March 12 1:30 p.m. GRAND BALLROOM CENTER

Update on Pathology of the Stomach

Moderator: Harry S. Cooper, Fox Chase Cancer Center, Philadelphia, PA

1:30 From Babel to Houston - via Sydney. The Continuing Saga of the Classification of Gastritis
Robert M. Genta, Baylor College of Medicine, Houston, TX

2:00 Polyps of the Stomach
Dale C. Snover, University of Minnesota, Minneapolis, MN

2:30 Markers of Precancerous Gastric Lesions
Pelayo Correa, Louisiana State University Medical Center, New Orleans, LA

3:00 Recess

3:30 Miscellaneous Forms of Gastritis
David Owen, University of British Columbia, Vancouver, BC

4:00 Gastric Involvement by Low Grade Lymphomas: Differential Diagnosis and Clinical Implications
Nancy Lee Harris, Harvard Medical School, Boston, MA

4:30 Discussion and Questions

Cap polyposis – an unusual cause of diarrhoea

A P Campbell, C A Cobb, R W G Chapman, M Kettlewell, P Hoang, B J Haot, D P Jewell

Nuffield Department of Pathology and Bacteriology, John Radcliffe Hospital, Oxford
A P Campbell

Department of Gastroenterology, John Radcliffe Hospital
C A Cobb
R W G Chapman
D P Jewell

Department of Surgery, John Radcliffe Hospital
M Kettlewell

Department of Gastroenterology, UCL Cliniques Universitaires St-Luc, Bruxelles
P Hoang

Department of Pathology, UCL Cliniques Universitaires St-Luc, Bruxelles
B J Haot

Correspondence to:
Dr A P Campbell, Nuffield Department of Pathology and Bacteriology, Level 4, Academic Street, John Radcliffe Hospital, Oxford OX3 9DU.

Accepted for publication
20 August 1992

Abstract

'Cap polyposis' is a poorly recognised condition with distinct clinical, sigmoidoscopic, and pathological features that may be confused with other inflammatory conditions of the large intestine including pseudomembranous colitis and idiopathic chronic inflammatory bowel disease. The pathogenesis is unknown but on the basis of the characteristic histological appearances, which are similar to those seen in situations where mucosal prolapse is the underlying mechanism, it has been suggested that the latter may be an important aetiological factor. Two cases are described. Histological features in the first (presence of intramucosal elastin) and clinical features in the second (rectal prolapse) support the above hypothesis.
(*Gut* 1993; 34: 562–564)

'Cap polyposis' was first described by Williams, Bussey, and Morson in 1985.[1] This poorly recognised condition has distinctive clinical, sigmoidoscopic, and pathological features. The pathogenesis is unknown but the histological appearances resemble those seen in solitary rectal ulcer syndrome or in areas of prolapse – for example, adjacent to diverticula or in relation to prolapsing colostomies. It has therefore been postulated that prolapse may be an important aetiological factor. Two cases are described in which the clinical and histological features may point to a possible pathogenic mechanism.

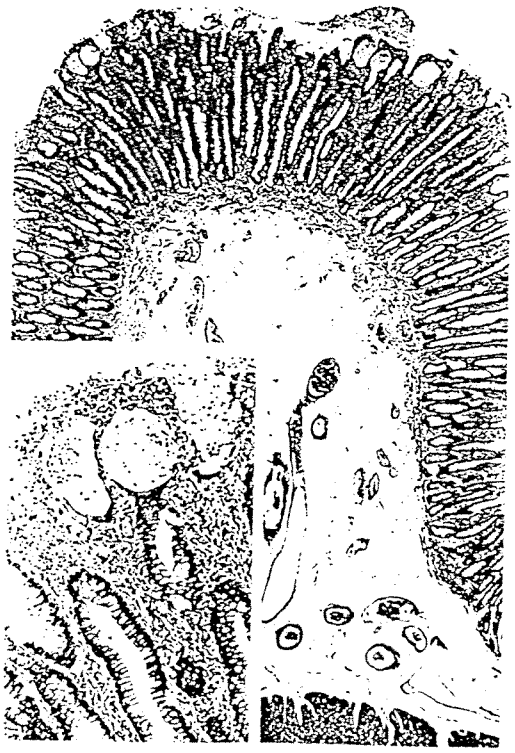


Figure 1: Low power view of a typical polyp with granulation tissue cap (high power inset) (original magnification ×17; high power inset ×87).

Case 1

A 68 year old white man presented in September 1988 with weight loss (approximately 1 st (6 kg) over the previous year), lower abdominal pain, and persistent watery diarrhoea. He had not noticed any blood or mucus. Barium enema showed marked spasm in the mid sigmoid colon associated with a localised area of diverticulosis. This was not, however confirmed subsequently. Initial biopsy specimens were thought to be suggestive of pseudomembranous colitis but examination of stool for *Clostridum difficile* toxin was negative and treatment with metronidazole was unhelpful. Later sigmoidoscopy and biopsy showed changes thought to be more suggestive of inflammatory bowel disease with 'pseudopolyps'. Treatment with sulphasalazine and prednisolone was unsuccessful and the patient underwent a left hemicolectomy in February 1990. The histological findings were multiple metaplastic polyps separated by normal mucosa with no evidence of inflammatory bowel disease.

Unfortunately the patient's symptoms recurred and 5 months later he presented again with a 2 month history of persistent diarrhoea which now contained copious amounts of mucus. Sigmoidoscopy showed multiple haemorrhagic polyps in the rectum. These occurred on the apices of the transverse mucosal folds and were separated by normal mucosa. Microscopic examination of biopsy specimens showed ulcerated inflamed mucosa with elongated tortuous crypts attenuated towards the mucosal surface. Review of the sections taken from the previous colectomy specimen showed polyps at the apices of exaggerated mucosal folds with similar histological features to those described above. They were covered by a 'cap' of inflammatory granulation tissue (Fig 1). The intervening mucosa was normal. The appearances were those of cap polyposis.

The patient was treated with hydrocortisone and mesalazine enemas. These were unsuccessful and a total colectomy with ileostomy was performed, from which he made an uneventful recovery. Macroscopic examination showed sessile haemorrhagic polyps on the apices of mucosal folds over the distal 12 cm of the specimen. The mucosa between the polyps and proximal to them was normal (Fig 2). Microscopic features were as described above. Sections from the two resection specimens were examined with an orcein stain for elastin fibres.[2] Intramucosal elastin was present in small quantities at the edges of some of the cap polyps (Fig 3).

Case 2

A 65 year old Belgian woman presented with a 6 month history of recurrent mucoid diarrhoea. Previous investigations had been inconclusive and a differential diagnosis of infection, solitary

FROM BABEL TO HOUSTON VIA SYDNEY

The Continuing Saga of the Classification of Gastritis

Robert M. Genta, M.D.

Departments of Pathology, Medicine and Microbiology and Immunology

VAMC and Baylor College of Medicine

Houston, Texas

Until a few years ago pathologists confronted with the evaluation of inflammatory conditions of the stomach could choose from a long and often confusing menu of classification systems. However, the range of clinically relevant diagnoses was painfully narrow. Consequently, many opted, and continue to opt, for a descriptive diagnosis. The result was the ubiquitous "acute and chronic inflammation" which, variously qualified by an array of modifiers, has long formed the core of most non-neoplastic diagnoses of mucosal biopsies from the gastrointestinal tract.

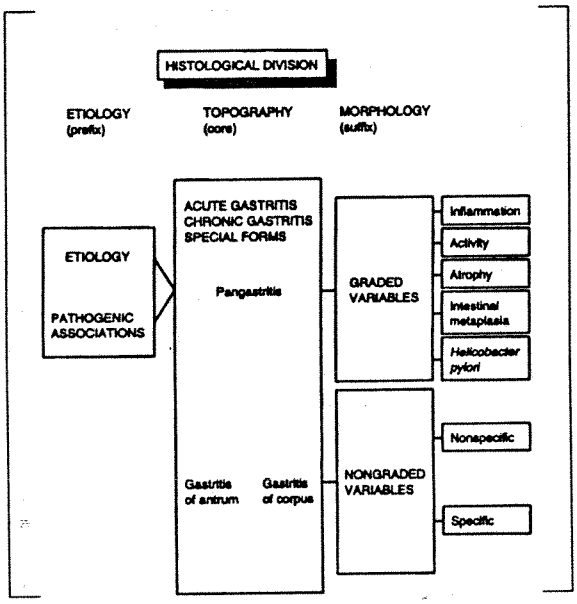
How did such a confusing situation arise? Modern concepts of histologic gastritis evolved in parallel with the development of techniques that permit access to the living patient's stomach. In 1947 Rudolf Schindler from the University of Chicago recognized acute and chronic gastritis and coined the terms "superficial" and "atrophic" gastritis, which have been incorporated in virtually every subsequent classification. When the modern fiberoptic endoscopes became widely available, Whitehead and his colleagues in Australia used biopsy material obtained endoscopically to develop what is now one most widely used classification of gastritis worldwide. Since 1970, not a single year has gone by without the development of a new classification or an improvement of an existing one. However, with some notable exceptions (the Whitehead and Correa classifications) few of these new classifications were ever used by anybody other than their proposer.

The Sydney System

The discovery of *Helicobacter pylori* in 1984, and the rapid demonstration that it was associated with most cases of so-called "idiopathic" chronic active gastritis, suggested the need for a novel system of classification that "would incorporate this new etiologic finding and at the same time be flexible enough to allow the integration of any future concepts." With this aim in mind, a group of mostly European gastroenterologists and pathologists formed a "working party" whose mandate was to generate a new comprehensive classification of gastritis. This new classification was presented at the 9th World Congress of Gastroenterology in Sidney, Australia, in 1990 and was named "The Sydney System."

The Sydney System consists of two branches or arms. The endoscopic arm

includes a series of descriptive categories which are applied to the endoscopic appearance of the gastric mucosa. This portion of the classification never became the subject of much controversy because it was never widely used.



The histologic arm (Fig. 1, above) includes three compartments (etiology, topography, and morphology), each of which may contain as many sub-categories as necessary.

For example, when performing a histologic diagnosis on two biopsy specimens from the antrum and the corpus from a patient with duodenal ulcer (Fig. 2), we would, according to the Sydney System, first try to determine the *etiology*. In this case our triple stain reveals large numbers of *H. pylori* in both specimens, so we know are dealing with *H. pylori* gastritis.

Next we evaluate the *severity* of gastritis by grading chronic inflammation, active inflammation, atrophy, intestinal metaplasia, and the density of bacteria. Using a scale from 0 (absent) to 3 (severe) we would say that the antral biopsy shows severe inflammation (both active and chronic), no atrophy, no intestinal metaplasia, and moderate *H. pylori* infection. The biopsy from the corpus shows a mild superficial mostly mononuclear infiltrate and *H. pylori*.

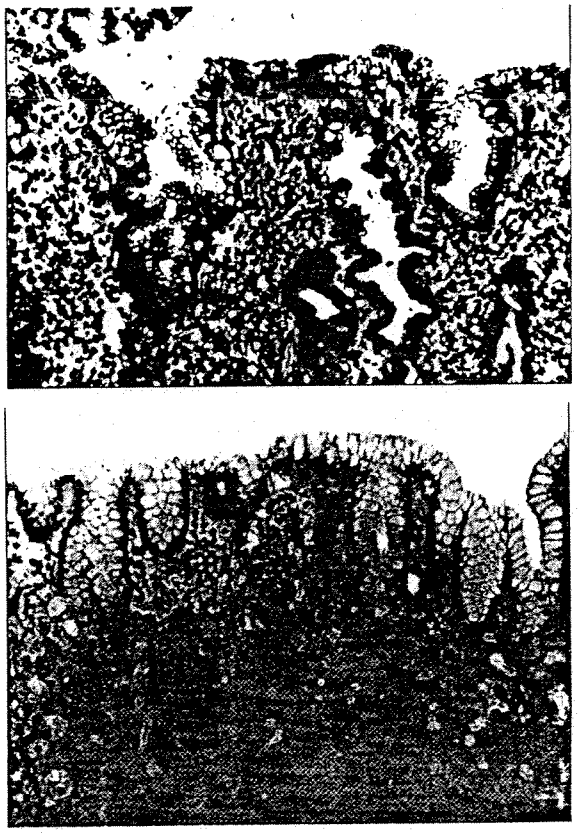


Figure 2. Antrum with severe *H. pylori* chronic active gastritis (upper) and mild superficial inflammation in the corpus (lower).

There is neither atrophy or intestinal metaplasia. Therefore, from the *topographic* viewpoint, we classify this as a predominantly antral gastritis, which, incidentally, is the type of gastritis most commonly associated with duodenal ulcer. Had we found the body as inflamed as the antrum, we would have called it with pangastritis. Using these building blocks, we have now generated a diagnostic string (Antral-predominant *H.*

pylori chronic active gastritis, severe) that provides information about the cause, the appearance, and the distribution of gastritis. We have also generated a useful diagnosis, because, in contrast to the trite "acute and chronic inflammation", the information provided can be used by the clinician for treatment and follow-up of the patient.

The Sydney System never became popular outside Europe. There are many reasons for this. First, it was published on an obscure Australian journal not available in most libraries. Second, as a European creation, it tended to overlook some entities, such as multifocal atrophic gastritis, that are more frequently diagnosed in other parts of the world. Finally, many pathologists in America and Asia felt left out and did not want to embrace a classification that claimed universality but had not been the product of a truly global commitment. As a result, in the past four years, only two or three papers from the United States and Canada have mentioned the Sydney System, all of them to criticize it.

The Houston Workshop

Convinced that the Sydney System could represent a usable framework on which to build a more acceptable classification of gastritis, we organized, with the collaboration of Michael Dixon from the University of Leeds, a workshop in Houston to discuss the histopathology of gastritis. In September 1994 we gathered 20 pathologists from various parts of the world (Fig. 3) known for their expertise in gastric pathology. As we planned the meeting, new ideas and suggestions came from the invited participants and many were incorporated into the agenda.

Figure 4. Houston Gastritis Workshop: the 20 participants - September 1994

Kenneth P. Batts, M.D., Rochester, Minnesota, USA
Pelayo Correa, M.D., New Orleans, Louisiana, USA
Beverly B. Dahms, M.D., Cleveland, Ohio, USA
Michael F. Dixon, M.B., B.S., Leeds, United Kingdom
M. Isabel Filipe, PhD, F.R.C.Path., London, United Kingdom
Robert M. Genta, M.D., Houston, Texas, USA
Rodger C. Haggitt, M.D., Seattle, Washington, USA
Jules Haot, M.D., Brussels, Belgium
P.K. Hui, M.B., B.S., Hong Kong
Juan Lechago, M.D., Ph.D., Houston, Texas, USA
Klaus Lewin, M.D., Los Angeles, California, USA
Johan A. Offerhaus, M.D., Amsterdam, The Netherlands
Ashley B. Price, M.D., Harrow, United Kingdom
Sixto Recavarren, M.D., Lima, Peru
Robert H. Riddell, M.D., Hamilton, Ontario, Canada
Pentti Sipponen, M.D., Helsinki, Finland
Enrico Solcia, M.D., Pavia, Italy
Manfred Stolte, M.D., Bayreuth, Germany
Hidenobu Watanabe, M.D., Niigata, Japan
John H. Yardley, M.D., Baltimore, Maryland, USA

A particularly important contribution came from John Yardley. He suggested that we attempt to agree on a common terminology of gastritis. To this end, he invited all participants to provide definitions of the terms most commonly used when dealing with the stomach. The list, further enriched by the individual contributors, included such apparently well-established concepts as antrum, fundus and active inflammation, as well as less clearly defined terms such as atrophy and dysplasia.

Thus, the establishment of a common terminology became our first goal. Our second goal was to decide whether the

Sydney System was it still usable, perhaps with revision and updating, or did it need to be replaced. Third, feeling that one of the reasons for the Sydney System's lack of appeal was the choice of journal on which it was originally published, we agreed that if we succeed to arrive at a consensus, we would disseminate the information to a worldwide audience. We also vowed to address primarily those who are going to use a histopathological classification of gastritis: pathologists.

The Houston Workshop began with establishing agreement on certain definitions. This included both anatomic and pathologic terms (such as acute and chronic gastritis, atrophy, dysplasia, metaplasia). Although this might seem a sophomoric matter, we found that there were considerable differences among pathologists in the interpretation of these and other terms.

Another key contribution to the success of the workshop came from Pelayo Correa who, during one of the initial planning meetings, suggested the inclusion of a pre-workshop slide exchange. Such an exchange would facilitate the standardization of definitions, grading, and classification of gastritis. Another aim of this exchange was to see, for example, whether there were geographic differences in the manifestations of *H. pylori* gastritis, to discuss the special forms of gastritis, such as lymphocytic and granulomatous gastritis, and to test whether the grading system incorporated in the Sydney system was reliable. Most importantly, however, we wanted to have a concrete base for our discussion.

To implement the slide exchange, each participant was asked to provide a representative slide of an entity that they knew well or that they thought should be included because it is controversial. I collected all the slides, coded them, and then sent them to each of the participants. Their task was to make a diagnosis using whatever terms or classification they preferred and to grade the inflammatory features according to a scale derived from the Sydney System.

Results of the slide exchange

Diagnosis: To be useful, a classification system must provide a diagnosis that has biologic significance and is reliable - that is, reproducible. That led us to ask whether it is efficient and effective to leave the choice of the classification system to the individual pathologist? Mike Dixon, who collated the results of the slide exchange and did the statistical analysis, provided a diplomatic answer to that question, noting that the diagnoses "reflected the individual bias among observers toward differing morphologic and etiologic classifications." Translated into plain English, that means the workshop's pathologists had widely divergent opinions on many of the diagnoses. These results clearly suggested that a globally accepted classification system is necessary if clinicians and researchers from various parts of the world are to interpret each other's diagnoses and data.

Grading: The results of grading are even more difficult to express in diplomatic language. With lesions in the antrum, agreement on chronic inflammation, activity (neutrophils), epithelial degeneration, and atrophy hovered around 50%. For intestinal metaplasia, which should be a straightforward entity - it is either present or absent - we agreed only 73% of the time. Agreement was no better with lesions in the body of the stomach: It ranged from 45% on chronic inflammation to 66% on intestinal metaplasia.

Rather than viewing these results as an indictment of grading *per se*, we saw these inconsistencies as an indication that when inadequate instructions on how to grade, poor standards and dismal agreement are to be expected. We had deliberately avoided giving the participants specific guidelines on the meaning of mild, moderate and severe, leaving it to them to interpret these terms. The results convinced us indicate that strict criteria must be provided if some degree of uniformity is to be expected.

Classification: We also asked participants whether they thought the Sydney system should be amended, and if so, how. As Bohrod has noted, "Classification should be an arrangement of the elements of disease into groups or sets according to some consistent point of view." Some of the pathologists who were not involved in the original drafting of the Sydney System felt that it did not meet this definition. For example, its morphologic classification did not acknowledge the distinction between active and inactive, superficial and deep, or atrophic and nonatrophic gastritis. Nor did it distinguish focal, multifocal, and diffuse metaplastic gastritis. Hence, there was no place in the System for the multifocal atrophic gastritis, an entity that seems to be more common in South America.

Thus, it is not surprising that we received a wide variety of suggestions, including advice to abandon the System entirely. We decided not to go that far, rather, we reached a broad consensus that the Sydney System may be quite valuable if not as the ultimate classification of gastritis, certainly as a comprehensive and uniform reporting system. However, we also agreed that the System needed specific additions and changes.

The Revised Sydney System (NOT to be known as the "Houston System")

In agreement with our initial decision to disseminate the results of this workshop to a wide audience of pathologists, we are currently preparing a major article that will describe in detail the revised Sydney System and provide easy-to-follow guidelines for pathologists and for clinicians who interpret the results of gastric biopsies reported in the System's language. This article will appear within the next few months on a major international pathology journal. A tutorial exploring some of the controversies we encountered at the slide exchange will be published on Modern Pathology. At the time of this writing (November 1994) I can only briefly outline the major changes that we hope will make the System more useful and more widely accepted. I hope that by March 1995 the articles will either have been published or at least be in advanced state of "in press."

Definitions: A glossary of gastritis will be included in the report. Anatomical and pathological terms used in the Sydney System have been defined according to the consensus reached at the Houston Workshop. Thus, when a pathologist writes "active inflammation of the cardia," every other pathologist who uses the System will know exactly what that expression means.

Grading: A new comprehensive guide to grading the five basic features of gastritis (density of *H. pylori*; active inflammation; chronic inflammation; atrophy; and intestinal metaplasia) will be provided. Rather than relying on inefficient verbal explanations for "mild," "moderate" and "severe", a series of visual-analog drawings will provide pathologists with a scheme to which they can constantly refer.

Additional entities: The type of gastric atrophy known in America as Multifocal Atrophic Gastritis (MAG) will be incorporated into the topographic and etiologic branches of the System.

Recommendations: Some of the participants in the Houston Workshop made a compelling case for distinguishing and reporting the various types of intestinal metaplasia. Patients with Type III (incomplete) may need close follow-up because they may be at a much greater risk than the general population for gastric carcinoma. Specific recommendations on where to biopsy the gastric mucosa in order to maximize information on this and other aspects of gastritis will be clearly presented.

The Endoscopic Arm: Based on the lack of enthusiasm displayed by our clinical colleagues and the absence of correlation between the endoscopic and histologic appearance of the gastric mucosa, we decided to leave this part of the Sydney System out of the revised version. A meeting of pathologists and gastroenterologists is being planned to discuss whether this portion of the classification should be resurrected.

Where do we go from here?

While we believe that we have improved the Sydney System, the value of the revised version can be ascertained only through testing. For that reason, we are organizing another slide exchange to take place during the next two years. The exchange will expanded to nonspecialists, because in the end, nonspecialists most frequently diagnose gastritis and other ailments of the gastrointestinal tract. We will then perform a statistical evaluation of the usefulness and consistency of the revised Sydney System. Our goal is to present the results of this new endeavor in Yokohama under the sponsorship of the Japanese Gastroenterologic Society in 1996.

SUGGESTED READING

Correa P. Chronic gastritis: A clinico-pathological classification. *Am J Gastroenterol* 1988;83:504-509.

Genta RM, Robason GO, Graham DY: Simultaneous visualization of Helicobacter pylori and gastric morphology: a new stain. *Human Pathology* 1994;25:221-226

Genta RM, Graham DY: Comparison of the biopsy sites for the histopathologic diagnosis of Helicobacter pylori:a topographic study of H. pylori density and distribution. *Gastrointestinal Endoscopy* 1994;40:342-345.

Misiewicz JJ: The Sydney System: a new classification of gastritis. Introduction. *J Gastroenterol Hepatol* 1991;6:207-208.

Price AB: The Sydney System: histological division. *J Gastroenterol Hepatol* 1991;6:209-222.

Price AB, Misiewicz JJ: Grading and classification of chronic gastritis: the response of the working party `letter: *Gastroenterology* 1992;103:1116-1117

Rubin CE: Histological classification of chronic gastritis: an iconoclastic view. *Gastroenterology* 1992;102:360-361

Updated information on the upcoming publications mentioned in the text will be provided during the conference.

POLYPS OF THE STOMACH

Dale C. Snover, M.D.
University of Minnesota Hospital

Polyps of the stomach are an often confusing area for the general surgical pathologist. This is in part because of lack of uniform terminology and rarity of most types of polyps. Several of the epithelial polyps are seen with regularity in general practice and should be readily recognizable, however.

Polyps of the stomach can be divided into epithelial, mesenchymal, lymphoid and the always popular "other" categories, with benign and malignant varieties occurring in both groups. I will confine my discussion to the benign polyps, since the commonest malignant polypoid lesions (i.e. adenocarcinoma) is generally readily recognizable.

EPITHELIAL POLYPS

The benign epithelial polyps make up the most common polypoid lesions of the stomach. As a practical matter *hyperplastic polyps, fundic gland hyperplasia and adenomas* make up more than 90% of the group although there are numerous other benign epithelial polyps that may be seen occasionally. General features of the benign polyps are listed in Table 1.

Hyperplastic polyp

Hyperplastic polyps have been reported in the literature by a bewildering variety of names including regenerative polyps, hyperplastic-adenomatous polyps, adenomatous polyps, hyperplasiogenous polyps and just plain benign polyps (1,3). It is important to note that they probably have no pathogenetic relationship whatsoever to the hyperplastic polyp of the colorectum. They make up approximately 70-90% of all gastric polyps (1). Hyperplastic polyps are seen in Cowden's syndrome, although given the rarity of the latter condition the association could be simply fortuitous (4,5).

These polyps are usually multiple, sessile lesions of variable size, often with a central umbilication. Occasional larger examples are polypoid. They are accompanied by atrophic gastritis in 75% or more of cases. Recent data has suggested a relationship in some cases to Helicobacter infection, although this topic has not been extensively studied (6). They are histologically characterized by thickening of the mucosa by elongation of the foveolae, which are often dilated resembling retention polyps. This similarity is further enhanced by an edematous, often inflamed lamina propria. The glandular portion of the mucosa is generally of antral type, even if the polyps is located in the body or fundus, although occasionally body-type glands are seen. The muscularis mucosae is usually hyperplastic as well with delicate bands of muscle extending randomly into the lamina propria toward the surface. There is often erosion of the surface with reactive atypia that can at times become alarmingly atypical mimicking neoplastic change. Since true neoplastic change can occur in these lesions, distinction must be made on the basis of associated clearly reactive epithelium (i.e. cuboidal epithelium with enlarged nuclei with distinct central nucleoli), ulceration, inflammation and/or granulation tissue in the lamina propria. True neoplastic change is not associated with these features and usually is more extensive than reactive atypia.

Biopsy diagnosis can be difficult since all of the above mentioned features may not be seen

in a single piece. In such a case the biopsy fragments must be mentally combined to produce the complete picture. The histological picture of Menetrier's disease is very similar to that of hyperplastic polyps, although the distinction can usually be made on the basis of the gross description of the lesion. There is some possible overlap in the cases of extremely large hyperplastic polyps and so-called limited Menetrier's disease.

An association between hyperplastic polyps and carcinoma has been proposed (7-9). Although occasional cases of carcinoma are seen in hyperplastic polyps, the risk of development of carcinoma would appear to be in the general range of that of the underlying atrophic gastritis (9b). Given recent suggestion of an association with Helicobacter and disappearance of polyps following treatment of the Helicobacter, careful examination for this organism with appropriate treatment would appear prudent in all cases (6). The presence of hyperplastic polyps is not an indication for prophylactic gastrectomy, something suggested in older literature with no justification (9).

Foveolar hyperplasia

This term applies to a probable precursor of the hyperplastic polyp (1). Foveolar hyperplasia is characterized by elongation of the foveolar portion of the mucosa without the splaying of the muscularis mucosae, edema, and inflammation typically seen in hyperplastic polyps. Since foveolar hyperplasia occurs in the same setting as hyperplastic polyps, it probably represents a lesser degree of reparative activity. Reactive changes around anastomosis sites and bile reflux gastritis produce an identical picture.

Fundic gland hyperplasia

Fundic gland hyperplasia (FGH)(also known as fundic gland polyp and cystic hamartomatous gastric polyp) is in our experience the second most common polyp of the stomach although the diagnosis is often overlooked since it may be difficult on biopsy to distinguish these lesions from normal body or fundic mucosa without a clinical history. FGH constitute at least 13% of benign gastric polyps. These polyps are the typical polyp seen in the stomach in familial adenomatous polyposis and Gardners syndrome, although the majority of cases are sporadic (10-16).

FGH usually presents as a myriad of 2-3 mm sessile lesions coating the body and fundus. There in general are no other lesions present. Histologically FGH is characterized by expansion of the glandular portion of the mucosa with normal foveolae. Although when seen in resected stomachs these lesions can be identified by the thickening relative to the adjacent mucosa, on biopsy this thickening cannot be recognized. Therefore these lesions may be mistaken for normal mucosa. If there is a clinical description of multiple sessile polyps, biopsy showing fundic mucosa should be considered consistent with fundic gland polyposis. Althouth the mucosa will sometimes appear to be totally nomal body-type mucosa, in most cases there will be dilated glands creating small cysts lined with parietal and chief cells, a nearly pathognomonic feature of these polyps on biopsy. The cysts are the most useful clue to diagnosis although they are not always seen. Occasional cysts lined with foveolar epithelium may be seen as well, but should not be confused with hyperplastic polyps since there are no other accompanying features of that condition. The mucosa adjacent to these lesions is generally normal without inflammation. No therapy is

required other than diagnostic biopsy. Since these lesions are associated with FAP, a reminder to that effect should be included in reports of this lesion.

Adenoma

Adenomas of the stomach are in most ways identical to similar lesions of the colorectum, although considerably less common in the United States. They constitute from 10 to 25% of gastric polyps. They can be divided into tubular, tubulovillous and villous forms. There is a relatively high rate of conversion of adenomas into carcinoma, although the majority of carcinomas of the stomach do not appear to arise in adenomas. Although adenomas may occur in familial adenomatous polyposis and its associated Gardners syndrome, fundic gland hyperplasia is much more common (11).

Adenomas are usually solitary and located in the antrum. They are usually associated with atrophic gastritis and not uncommonly are accompanied by more typical hyperplastic polyps elsewhere in the stomach. Histologically they are defined by their epithelium which is pseudostratified with elongated atypical nuclei and increased mitotic activity. Ulceration and erosion are uncommon. High grade dysplasia and frank invasive carcinoma may be seen.

Given the premalignant nature of these lesions, complete excision is recommended in all cases. In stomachs with multiple hyperplastic polyps as well as adenomas, excision of all pedunculated lesions and lesions larger than 1 cm should be undertaken if possible.

Mixed hyperplastic-adenomatous polyps

True mixed neoplastic-hyperplastic polyps are occasionally encountered (1). The neoplastic portion generally occupies the entire surface of the lesion, and is sharply demarcated from the underlying hyperplastic areas. I suspect that this phenomenon represents neoplastic transformation occuring randomly on a preexisting hyperplastic polyp, since it is too rare of a finding to indicate any intrinsic preneoplastic potential to hyperplastic polyps. The major difficulty with this lesion is in distinguishing it from a hyperplastic polyp with reactive atypia. This distinction is discuss above with the hyperplastic polyps. The significance of these lesions is similar to that of adenomas.

Retention polyps

Retention polyps occur in the stomach under three circumstances: solitary, multiple as part of retention polyposis and as part of the Cronkhite-Canada syndrome (17-19). Retention polyps are characterized by dilated gland-like spaces in an edematous and inflamed lamina propria. This picture is very similar to that of hyperplastic polyps, however, and differs mainly by a lack of splayed muscularis mucosae. Most solitary retention polyps of the stomach probably represent incompletely sampled hyperplastic polyps. Retention polyposis cases demonstrate multiple retention polyps throughout the GI tract and hence are diagnosable by looking at the overall pattern of disease in the patient. Cronkhite-Canada syndrome is characterized by multiple polyps that have an appearance similar to retention polyps although in some cases the degree of dilatation is not as great as typical retention polyps and there may be eosinophilia associated with the polyp (19). It is said that the mucosa is abnormal even between polyps, with glandular dilatation even in flat mucosa. As with retention polyposis, this is a condition involving more than just the stomach,

so the final diagnosis rests on overall assessment of the patient.

Hamartomatous polyps

Hamartomatous polyps occur in the stomach sporadically and in the Peutz-Jegher syndrome. These are characterized by tree-like branching of the muscularis mucosae (differing from the splaying of the muscularis in hyperplastic polyps by the thickness and regularity of the muscle bands) covered with normal (more-or-less) mucosa (20,21).

Other epithelial polyps

The other epithelial polyps of the stomach, antral gland hyperplasia and foveolar adenoma, are curiosities with only a few described cases (1).

Mesenchymal polyps

The major mesenchymal polyp of the stomach is the inflammatory fibroid polyp (IFP), a lesion of uncertain pathogenesis with a very characteristic histology (22,23). IFPs tend to be solitary lesions in the antrum, and are often pedunculated. The superficial mucosa overlying the polyp is generally intact, with the polyp being formed by a proliferation of myofibroblasts, thick walled blood vessels and eosinophils predominantly in the submucosa. There is a characteristic onion-skinned pattern of growth of the myofibroblasts around the vessels, leading to a neuroid appearance to the lesion. Early descriptions suggested that this was in fact a neural tumor, a theory that has been set aside by modern immunohistochemical techniques (22). IP studies demonstrate staining for actin and vimentin, with staining for vascular markers limited to the endothelium of clear-cut vessels. Neural markers are negative. It is not clear as to whether IFP represents a reactive process or a neoplasm, but excision is curative.

Smooth muscle and stromal tumors will occasionally present as polyps, although biopsy diagnosis is rare since the polyp produced is sessile and not amenable to snare excision. Since criteria for malignancy of these tumors is based on features not determinable on biopsy (i.e. size, necrosis, mitotic count), excision is generally required for diagnosis as well as treatment.

Lymphoid lesions

Lymphoid hyperplasia and lymphoma may present as polypoid lesions. Distinction on biopsy is very difficult. In general the more monomorphic the infiltrate is the more worrisome, although the presence of germinal centers and a mixed population does not assure that a lesion is benign. The presence of lymphoepithelial lesions (i.e. infiltration of crypts by the lymphoid cells) is suggestive of low-grade mucosal-associated lymphoma (maltoma), although final diagnosis usually requires a large piece of tissue (i.e. not a forceps biopsy) and formal cell marker studies.

Pancreatic heterotopia

Occasionally pancreatic heterotopia and its probable relative adenomyosis of the stomach can present as polypoid lesions (24,25). These processes occur in the antrum and may lead to pyloric outlet obstruction in the neonate. Pancreatic heterotopia is characterized by the presence of islands of pancreatic tissue in the submucosa and muscularis. Adenomyoma resembles pancreatic heterotopia without pancreatic acini, i.e. it consists of ducts surrounded by muscle of

the muscularis. Both conditions are benign.

References

1. Snover DC. Benign epithelial polyps of the stomach, in Sommers SC, Rosen PP, Fechner RE (eds.): *Pathology Annual, Part 1.* Norwalk, CT, Appleton-Century-Crofts, 1985, pp 303-329.

2. Appelman HD. Localized and extensive expansions of the gastric mucosa: mucosal polyps and giant folds, in Appelman HD, ed. *Pathology of the Esophagus, Stomach and Duodenum,* Churchill Livingstone, New York, NY, 1984, pp79-119.

3. Neimark S, Rogers AI. Gastric polyps: A review. Am J Gastroenterol 77:585-587;1982.

4. Hizawa K. Iida M. Matsumoto T. Kohrogi N. Suekane H. Yao T. Fujishima M. Gastrointestinal manifestations of Cowden's disease. Report of four cases. Journal of Clinical Gastroenterology 18:13-8;1994.

5. Haggitt RC, Reid BJ. Hereditary gastrointestinal polyposis syndromes. Am J Surg Pathol 10:871-877;1986.

6. Veereman Wauters G, Ferrell L, Ostroff JW, Heyman MB.Hyperplastic gastric polyps associated with persistent Helicobacter pylori infection and active gastritis. American Journal of Gastroenterology. 85:1395-1397, 1990

7. Orlowska J. Tomecki R. Butruk E. Carcinoma in hyperplastic polyps of the stomach An underestimated possibility. Case reports. APMIS 99:398-404;1991.

8. Yamaguchi K. Shiraishi G. Maeda S. Kitamura K. Adenocarcinoma in hyperplastic polyp of the stomach. American Journal of Gastroenterology 85:327-8;1990.

9. Roxburgh RA. The case for total gastrectomy in multiple polyposis of the stomach. Gut 3:224;1962.

9b. Kamiya T, Morishita T, Asukura H, et al. Histoclinical long-standing followup study of hyperplastic polyps of the stomach. Am J Gastroenterol 75:275-281;1981.

10. Sipponen P, Laxen F, Seppala K. Cystic "hamartomatous" gastric polyps: A disorder of oxyntic glands. Histopathology 7:729;1983.

11. Watanabe H, Enjoji M, Yao T, Ohsato K. Gastric lesions in familial adenomatosis coli: Their incidence and histologic analysis. Hum Pathol 9:269;1978.

12. Jarvinen H, Nyberg M, Peltokallio P. Upper gastrointestinal tract polyps in familial

adenomatosis coli. Gut 24:333;1983.

13. Burt RW, Berenson MM, Lee RG, et al. Upper gastrointestinal polyps in Gardner's syndrome. Gastroenterology 86:295;1984.

14. Iida M, Yao T, Watanabe H, et al. Fundic gland polyposis in patients without familial adenomatous coli: Its incidence and clinical features. Gastroenterology 86:1437-1442;1984.

15. Kinoshita Y, Tojo M, Yano T, et al. Incidence of fundic gland polyps in patients without familial adenomatous polyposis. Gastrointest Endosc 39:161-163;1993.

16. Marcial MA, Villafana M, Hernandez-Denton J, et al. Fundic gland polyps: Prevalence and clinicopathologic features. Am J Gastroenterol 88:1711-1713;1993.

17. Subramony C. Scott-Conner CE. Skelton D. Hall TJ. Familial juvenile polyposis. Study of a kindred: evolution of polyps and relationship to gastrointestinal carcinoma. American Journal of Clinical Pathology 102:91-7;1994

18. Sachatello CR, Pickren JW, Grace JT. Generalized juvenile gastrointestinal polyposis. Gastroenterology 58:699;1970.

19. Daniel ES, Ludwig SL, Lewin KJ, et al. The Cronkhite-Canada syndrome: An analysis of clinical and pathologic features and therapy in 55 patients. Medicine 61:293;1982.

20. Dormandy TL. Gastrointestinal polyposis with mucocutaneous pigmentation (Peutz-Jeghers syndrome). N Engl J Med 256:1093, 1141, 1186;1957.

21. Horn RC, Payne WA, Fine G. The Peutz-Jeghers syndrome. Arch Pathol 76:29;1963.

22. Kolodziejczyk P, Yao T, Tsuneyoshi M. Inflammatory fibroid polyp of the stomach. A special reference to an immunohistochemical profile of 42 cases. American Journal of Surgical Pathology 17:1159-68;1993.

23. Adachi Y, Mori M, Iida M, Tsuneyoshi M, Sugimachi K. Inflammatory fibroid polyp of the stomach. Report of three unusual cases. Journal of Clinical Gastroenterology 15:154-8;1992.

24. Barbosa JJ de C, Dockerty MB, Waugh JM. Pancreatis heterotopia. Review of the literature and report of 41 authenticated surgical cases of which 25 were clinically significant. Surg Gynecol Obstet 82:527-542,1946.

25. Zarling EJ. Gastric adenomyoma with coincidental pancreatic rest: a case report. Gastrointest Endoscopy 27:175-177, 1981.

Table 1
Benign Epithelial Polyps of the Stomach

Polyp Type	Percentage of all benign polyps	Multiple or solitary	Risk of carcinoma	Polyposis syndromes
Hyperplastic	75-90%	>60%	Low (<1%)	Cowdens syndrome
Foveolar hyperplasia	Common, not necessarily as polyps	>70%	Probably fortuitous	
Fundic gland polyp	13-75%	>90%	Low to none	Familial adenomatosis coli, Gardners syndrome
Adenoma	10-25%	~15%	High (6-75%)	FAP
Mixed hyperplastic-adenomatous	4%	>60%	High	
Retention	<1%	NA	?, probably none	Juvenile polyposis, Cronkhite-Canada
Hamartomatous	<1%	Most	?, minimal	Peutz-Jeghers
Antral gland	<1%	?	?	

MARKERS OF PRECANCEROUS GASTRIC LESIONS

Pelayo Correa, M.D.
Louisiana State University Medical Center
New Orleans, LA

The accumulated experience of pathologists throughout the world has indicated that gastric carcinomas of the "intestinal" type are preceded by a series of lesions of the gastric mucosa which constitute the precancerous process. Although semantic difficulties have created problems of interpretation, recently they have been largely resolved when pathologists practicing in different parts of the world have discussed their collective experience. It is becoming clear that a disease complex characterized by focal atrophy, namely Multifocal Atrophic Gastritis (MAG) is the most common background in which gastric carcinoma makes its appearance. The sequential stages of the process are: 1) nonatrophic chronic gastritis; 2) multifocal gland loss (atrophy), 3) intestinal metaplasia type I, also called "complete" or small intestinal type; 4) intestinal metaplasia type III, also called "incomplete" or "colonic type" and 5) dysplasia. These stages are identified with hematoxylin-eosin stains and are the best "markers" of the precancerous process. They serve as the "gold standard" to evaluate other markers of the precancerous process and have been well recognized and described in the medical literature (Morson, 1955; Cuello, 1979; Jass, 1983; Filipe, 1985; Matsukura, 1980).

In populations at high risk of gastric cancer, the most frequent lesion found is intestinal metaplasia, but its prevalence is so high that it is of limited clinical value

since it does not identify persons at higher risk. More refined markers are therefore needed, which can be classified in 4 main groups: mucins, blood group related antigens, markers of replication and molecular alterations.

Mucins

The normal stomach secretes neutral mucins which stain positive with the PAS techniques. They occupy the cytoplasm of the surface epithelium and the antral glands. The cells of the glandular necks behave as stem cells and contain minute amounts of gastric and intestinal mucins.

In type I intestinal metaplasia goblet cells make their abnormal appearance in the gastric mucosa and their cytoplasm contains abundant acid sialomucins which are the normal secretions of small intestinal epithelium and stain positive with Alcian Blue at pH 2.5. In type III metaplasia acid sulfated mucins make their appearance, either in goblet cells or in the columnar "absorptive" cells which separate the goblet cells. Sulfated mucins are normal in the large intestine. Their appearance in the stomach may be accompanied by morphologic irregularities of the metaplastic glands, which may be equivalent to a mild grade of dysplasia (Masukura, 1980, Filipe, 1986). The presence of sulfomucins in goblet cells in these lesions carriers a 5.7 fold increase in the relative risk of gastric carcinoma (Filipe, 1994).

Blood group related antigens

The gastric epithelium synthesizes blood group antigens. The most studied are the ABH and the Lewis systems. They are carbohydrate moieties structurally

integrated to the mucous secretions and are important in cell recognition, differentiation and intercellular cohesion. The Lewis system is controlled by the Lewis and by the secretor gene as illustrated in the diagram. Approximately 80% of subjects are of the Lewis (a-b+) phenotype. In the gastric precancerous process subjects of this phenotype may develop a blockage of the synthesis of Le^b antigen resulting in an accumulation of its precursors, which then follow an anomalous pathway and express Le^a antigen. Monoclonal antibodies are available to recognize Lewis antigens. Of special interest is the abnormal expression of Le^a antigens in Lewis (a-b+) subjects, which together with abnormal expression of sulfomucins are good markers of type III metaplasia and dysplasia. These changes allow the identification of a subset of patients with intestinal metaplasia which carry a higher risk of carcinoma (Torrado, 1992).

Cell replication markers

Cell replication is a sine qua non in gastric carcinogenesis. Excessive replication ("hyperproliferation") increases the cancer risk and has the potential of fixing in the cell lineage mutations produced by internal or external influences. Different systems are available to assess cell replication. H_3 thymidine incorporation studied by autoradiography was the only method available for many years and gives excellent results (Lipkin, 1985). It requires incubation of several weeks and utilizes radioactive materials. Bromodeoxyuridine avoids the need for radioactive material and requires shorter incubation (Richter, 1992). The nucleolar organizers stained with colloidal silver nitrate, are a good index of proliferation and

ploidy alterations (Correa, 1994). Several cyclins, proteins synthesized during the S phase of the cell cycle, are available for immunochemical stains with monoclonal antibodies. The 2 most used and commercially available are the Proliferating Cell Nuclear Antigen (PCNA) and the Ki67 antibody. PCNA has a half life of approximately 20 hours while Ki-67 has a half life of approximately 3 hours.

Molecular markers

Multiple markers of molecular alterations have been applied to gastric carcinomas and to precursor lesions. The field is evolving and the utility of each marker remains to be defined. One early marker described is the tpr-met transition. It detects a chimeric sequences in which the translocated promoter region of chromosome 1 binds with the met oncogene of chromosome 7 (Soman, 1991). The k-ras oncogene has been associated with intestinal metaplasia (Kihana, 1994). p53 alterations are involved with dysplastic changes in previously metaplastic glands (Shiao, 1994). The c-erb-2 oncogene has been associated with aggressive tumors, as has the p53 protein. K-sam oncogenic has been associated with diffuse carcinomas (Correa, 1994). Special attention has been given to calcium dependent adhesion molecules, which may determine the mode of spread: diffuse carcinomas lack such molecules and their cells infiltrate the tissues individually; "intestinal" type carcinomas form glands which invade tissues in an expansive fashion (Tahara, 1993).

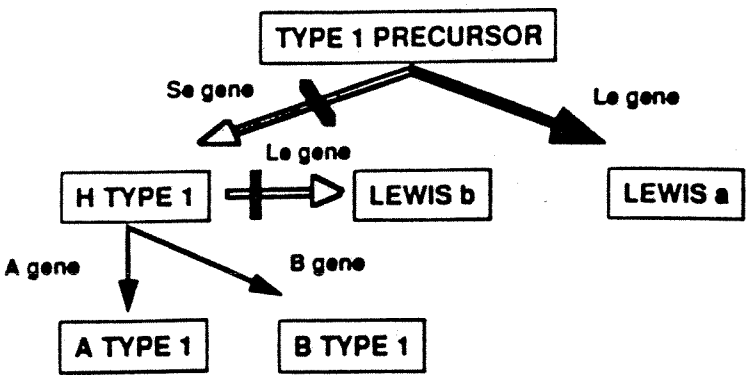


Figure 1. Diagrammatic representation of the biosynthesis of Lewis antigens. The *bars* intercepting the *arrows* represent the hypothetical points of blockage leading to abnormal expression of Le^a in individuals of Le(a−b+) phenotype. Se gene, secretor gene; Le gene, Lewis gene.

REFERENCES

Brenes F, Ruiz B, Correa P, et al. Helicobacter pylori causes hyperproliferation of the gastric epithelium: Pre- and post-eradication indices of PCNA. Am J Gastroenterol 88:1870-75, 1993.

Correa P. Chronic gastritis: A clinico-pathologic classification. Am J Gastroenterol 83:504-9, 1988.

Correa P, Haenszel W, Cuello C, et al. Gastric precancerous process in a high risk population: cross sectional studies. Cancer Res 50:4731-36, 1990.

Correa P, Ruiz B, Shi TY, et al. Helicobacter pylori and nucleolar organizer regions in the gastric antral mucosa. Am J Cl Path 101:656-60, 1994.

Correa P, Shiao YH. Phenotypic and genotypic events in gastric carcinogenesis. Cancer Res 54:1941s-1943s, 1994.

Cuello C, Correa P, Zarama G, et al. Histopathology of gastric dysplasia. Am J Surg Path 3:491-500, 1979.

Filipe MI, Patel M, Bogomeletz VW, et al. Incomplete sulfomucin secreting intestinal metaplasia. Gut 26:319-26, 1986.

Filipe MI, Muñoz, Matko I, et al. Intestinal metaplasia types and the risk of gastric cancer: a cohort study in Slorenia. Int J Cancer 57:324-29, 1994.

Jarvis O, Lauren P. On the role of heterotopias of intestinal epithelium in the pathogenesis of gastric cancer. Acta Path & Microbiol Scand 29:26-44, 1951.

Jass JR. A classification of gastric dysplasia. Histopathology 7: 181-193, 1983.

Kihana T, Tsuda H, Hirota T, et al. Point mutations of c-Ki-ras oncogene in gastric adenoma and adenocarcinoma with tubular differentiation. Jpn J Cancer Res 51:2926-31, 1991.

Lipkin M, Correa P, Mikol YB, et al. Proliferative and antigenic modifications of human epithelial cells in chronic atrophic gastritis. J Nat Cancer Inst 75:613-619, 1985.

Matsukura N, Susuki K, Kawachi T, et al. Distribution of marker enzymes and mucin in intestinal metaplasia in human stomachs in relation to complete and incomplete types of intestinal metaplasia to minute gastric carcinomas. J Natl Cancer Inst 65:231-240, 1980.

Morson, BC. Carcinoma arising in intestinal metaplasia in the gastric mucosa. Br J Cancer 9: 377-85, 1955.

Morson BC, Sobin LH, Grundman E, et al. Precancerous conditions and epithelial dysplasia in the stomach. J Clin Path 33:711-21, 1980.

Nagayo T. Dysplasia of the gastric mucosa and its relation to the precancerous state. Gann 72:813-823, 1981.

Richter F, Richter A, Yan K, et al. Cell preliferation in rat colon measured with bromodeoxyuridine, PCNA and ^{3}H thymidine. Cancer Epid Biomark Prevention 1:561-6, 1992

Shiao YH, Rugge M, Correa P, et al. p53 alterations in gastric precancerous lesions. Am J Path 144:511-17, 1994.

Silva S, Filipe MI. Intestinal metaplasia and its variants in the gastric mucosa of Portuguese subjects: a comparative analysis of biopsy and gastrectomy material. Human Path 17:988-95, 1986.

Sipponen P, Sepala K, Varis K, et al. Intestinal metaplasia with colonic type sulfomucins; its association with gastric carcinoma. Acta Path Microbiol Scand 88:217-24, 1981.

Soman NR, Correa P, Ruiz B and Wogan GN. The PPR-MET oncogenic rearrangement in human gastric carcinoma and precursor lesions. Proc Nat Acad Sci 88:4892-96, 1991.

Stemmermann GN, Hayashi T. Intestinal metaplasia of the gastric mucosa: A gross and microscopic study of its distribution in various disease states. Nat Cancer Inst 57:1027-35, 1976.

Tahara E. Molecular mechanisms of stomach carcinogenesis. J Cancer Res Clin Oncol 119:265-72, 1993.

Torrado J, Correa P, Ruiz B, et al. Lewis antigen alterations in gastric cancer precursors. Gastroenterology 102:424-30, 1992.

Torrado J, Correa P, Ruiz B, et al. Prospective study of Lewis antigen alterations in the gastric precancerous process. Cancer Epid Biomarkers Prev 1:199-205, 1992.

MISCELLANEOUS FORMS OF GASTRITIS

Dr. D.A. Owen
The University of British Columbia

This category of gastritis includes all forms of inflammation of the stomach that are not attributable to H. pylori infection. Miscellaneous forms of gastritis account for approximately 5% of cases of gastritis diagnosed by biopsy.

Acute Erosive Gastritis

This is a relatively common cause of upper gastrointestinal bleeding that is particularly common in patients hospitalized in the Intensive Care Unit. The causes include shock (mucosal hypoxia), drugs (especially NSAIDs) and alcohol, although some cases have no known provoking factor. The condition varies in severity and extent from a diffusely hemorrhagic mucosa containing large numbers of erosions to small numbers of erosions with no intervening hemorrhage.

An erosion is defined as an acute ulcer that does not penetrate the full thickness of the mucosa. They are usually 1-5 mm in diameter. Erosions contain a necrotic slough at the base and the adjacent lamina propria shows dilated capillaries with variable amounts of hemorrhage. Small numbers of neutrophils may be present. Between erosions, the mucosa may contain large amounts of hemorrhage into the lamina propria.

Suppurative Gastritis

This is an exceedingly rare condition that has a high mortality and is usually diagnosed at autopsy. It is the result of infection of the gastric wall by a pyogenic organism. Streptococci are the bacteria most frequently isolated, but other pathogens include E. coli and H. influenzae.

Histologically, there is intense edema, hemorrhage and a purulent infiltrate in the submucosa. Generally, the overlying mucosa is relatively intact and the infection does not spread to the muscularis propria. Gas-forming organisms produce submucosal bubbles and a gross appearance that has been termed emphysematous gastritis.

Autoimmune Gastritis

This condition is characterized by destruction of the specialized acid and enzyme-secreting cells of the fundic mucosa. The damage is thought to be predominantly cell-mediated, but humoral immunity, particularly antibodies to intrinsic factor, and parietal cells may play a role. Ultimately, the patients develop pernicious anemia. As far as the stomach is concerned, most patients are asymptomatic.

The early stages of autoimmune gastritis are not fully described. Some reports indicate a lymphoplasmacytic infiltration in the deeper glandular portion of the fundic mucosa. The late stages are characterized by a virtual total fundic gland loss and a profound complete intestinal metaplasia of the surface and pit lining mucosa. The antral mucosa is usually not atrophic, although in response to achlorhydria there may be a secondary hyperplasia of G-cells. The resulting hypergastrinemia causes hyperplasia of fundic ECL cells, which may ultimately result in carcinoid tumor formation. Usually, this takes the form of multiple microcarcinoids, although occasionally larger tumors occur.

In some texts, autoimmune gastritis is also called gastritis type A, to distinguish it from the antral gastritis of H. pylori, which is termed gastritis type B.

Reflux Gastritis

This is a relatively common condition and is probably underdiagnosed histologically. Endoscopically, the antral mucosa may be quite extensively congested, although the histologic lesions tend to be subtle. The changes are more frequently found in patients with a prior gastrectomy, but may also be encountered in the intact stomach.

Histologically, a low power view of the mucosa reveals elongation and tortuosity of the gastric pits, sometimes resulting in a corkscrew appearance. The pit lining and surface cells show cytoplasmic mucin loss, with nuclear enlargement and hyperchromasia. Within the lamina propria, there is superficial edema with dilated capillaries. Commonly, prominent tongues of smooth muscle extend upwards from the muscularis mucosa to reach the subsurface epithelium.

The lesion is considered to be the result of increased exfoliation from the mucosal surface. In reflux gastritis, this is presumably the result of epithelial damage by duodenal secretions. A similar appearance can also be encountered following drug therapy (particularly NSAIDs), which also produces increased exfoliation of surface cells. This pattern of gastritis is also called gastritis type C, or chemical gastritis.

Lymphocytic Gastritis

This entity has been described relatively recently, so that the full range of clinical and morphological manifestations is not yet identified. Some cases have been associated with H. pylori infection. Other cases have been associated with celiac sprue, although in most instances the cause is not known. It may represent an unusual host response to a variety of luminal antigens.

Mild forms of lymphocytic gastritis are asymptomatic and have a normal endoscopic appearance. In more florid cases, there may be chronic erosions (varioliform gastritis) or even giant mucosal folds with protein loss resembling Menetrier's disease.

Histologic changes consist of an infiltrate of lymphocytes into the surface epithelium, pit lining epithelium and superficial lamina propria. The lymphocytes are morphologically unremarkable small T-lymphocytes. Intra-epithelial clusters referred to as lympho-epithelial lesions are only rarely encountered.

It is my experience that some cases which would formerly be classified as Menetrier's disease are, in fact, examples of florid lymphocytic gastritis. This may explain some of the confusion in the literature pertaining to Menetrier's disease, particularly those cases which occur in children, are self-limited, or involve the duodenum. However, there is one recent report describing six cases in which Menetrier's disease and lymphocytic gastritis co-existed. The authors speculate that both conditions may have a common pathogenesis.

Eosinophilic Gastritis

Great care should be exercised in interpreting the presence of excess numbers of eosinophils in the gastric lamina propria. This finding may occur in a wide variety of clinical situations and is generally only considered significant if large numbers of eosinophils are present in sheets. Eosinophilic gastritis should be considered as a syndrome, rather than a specific disease entity. It has a number of causes. These include food allergy (particularly in children), allergy to drugs and parasitic disease. In addition, there is an idiopathic form of eosinophil infiltration termed eosinophilic gastroenteritis, which is characterized by massive segmental

eosinophil infiltration. Many of these cases involve the gastric antrum with or without an associated duodenal involvement. Eosinophils are present in the mucosa, gastric wall and serosa. These patients generally have a peripheral eosinophilia and respond well to corticosteroid therapy.

Non-infectious Granulomatous Gastritis

Three entities need to be considered under this heading: Crohn's disease, sarcoidosis and idiopathic granulomatous gastritis. On histologic grounds, it is often impossible to distinguish these entities. Crohn's disease tends to occur in young adults and is almost invariably accompanied by evidence of disease elsewhere in the gastrointestinal tract (particularly terminal ileum). As well as granulomas, there may be considerable non-specific inflammation, including small numbers of eosinophils. Sarcoidosis is commoner in Blacks and is generally accompanied by radiologic evidence of pulmonary involvement. By definition, idiopathic granulomatous gastritis consists of granulomatous inflammation confined to the stomach. In all of these conditions, granulomas may be found in the submucosa and muscularis propria, as well as in mucosa biopsies. They tend to affect mainly the antral portion of the stomach. With progressive transmural disease, this can lead to scarring and pyloric stenosis.

Other forms of gastritis

Inflammation of the stomach may occur in a large number of diseases that are relatively uncommon. These include infectious diseases, such as tuberculosis, systemic fungal disease, cytomegalovirus and syphilis. Non-infectious causes include graft-versus-host disease, collagenous gastritis and collagen vascular diseases.

References

Appelman HD. Gastritis: terminology, etiology and clinical pathological correlations. Hum Pathol 1994;25:1006-1019.

Laine L, Weinstein WM. Subepithelial hemorrhages and erosions of the human stomach. Dig Dis Sci 1988;33:490-503.

O'Toole PA, Morris JA. Acute phlegmonous gastritis. Post Grad Med J 1988;64:315-316.

Burman P, Kampe O, Kraaz W, et al. A study of autoimmune gastritis in the post partum period and at a 5-year follow up. Gastroenterology 1992;103:934-942.

Lewin K, Dowling F, Wright JP, et al. Gastric morphology and serum gastrin levels in pernicious anemia. Gut 1976;17:551-560.

Borch K, Renvall H, Kullman E, et al. Gastric carcinoid tumor associated with a syndrome of hypergastrinemic atrophic gastritis: a prospective analysis of 11 cases. Am J Surg Pathol 1987;11:435-444.

Sohala GM, King RF, Axon AT, et al. Reflux gastritis in the intact stomach. J Clin Pathol 1990;43:303-306.

Wyatt J, Dixon MF. Chronic gastritis: a pathogenetic approach. J Pathol 1988;154:944-951.

Haot J, Hamichi L, Wallez L, et al. Lymphocytic gastritis: a newly described entity. A retrospective endoscopic and histologic study. Gut 1988;29:1258-1264.

Haot J, Bogomoletz WV, Jouret A, et al. Menetrier's disease with lymphocytic gastritis. An unusual association with possible pathogenetic associations. Hum Pathol 1991;22:379-386.

Fahimi HD, Deren JJ, Gottlieb MD, et al. Isolated granulomatous gastritis: its relationship to disseminated sarcoidosis and regional enteritis. Gastroenterology 1963;45:161-175.

Blackshaw AJ, Levison DA. Eosinophilic infiltrates of the gastrointestinal tract. J Clin Pathol 1986;39:1-7.

Johnstone H, Morson BC. Eosinophilic gastroenteritis. Histopathology 1978;12:348-355.
Goldman H, Proujansky R. Allergic proctitis and gastroenteritis in children. Clinical and mucosal biopsy features in 53 cases. Am J Surg Pathol 1986;10:75-86.
Snover DC, Weisdorf SA, Vercelotti GM, et al. A histologic study of gastric and intestinal graft-versus-host disease following allogenic bone marrow transplantation. Hum Pathol 1985;16:387-392.

GASTRIC INVOLVEMENT BY LOW-GRADE LYMPHOMAS: DIFFERENTIAL DIAGNOSIS AND CLINICAL IMPLICATIONS

Nancy Lee Harris, M.D.
Department of Pathology
Massachusetts General Hospital
Harvard Medical School
Boston, MA

I. Lymphomas that may occur in the gastrointestinal tract [1]

B-CELL LYMPHOMAS

		Sites involved
Low-Grade		
	MALT type	**Stomach>SI=colon**
	Subtype: IPSID	SI
	Mantle cell	Colon> **stomach**>SI
	Follicle center lymphoma	SI> stomach>colon
	B-cell small lymphocytic lymphoma/CLL	Any site (rare)
High Grade		
	MALT	Stomach>SI>colon
	Large B-cell lymphoma, nodal type	SI>colon
	Burkitt's and Burkitt-like	SI (ileocecal)

T-CELL LYMPHOMAS (all high grade)

Intestinal T-cell lymphoma (+/- enteropathy)	SI (jejunum)>stomach
Other types of T-cell lymphoma	Any site

II. Defining features of low-grade B-cell lymphomas (from the R.E.A.L. Classification [2])

A. Marginal Zone B-cell Lymphoma:

1. Extranodal: Low-grade B cell Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT) Type (+/- monocytoid B cells)

2. Nodal: (+/- Monocytoid B cells) (provisional)

Synonyms:

Rappaport: (not specifically listed) WDL or WDL-plasmacytoid, IDL, ILL, PDL, mixed lymphocytic-histiocytic (nodular or diffuse)

Kiel: monocytoid B-cell, immunocytoma (some cases previously classified as centroblastic/centrocytic or centrocytic)

Lukes-Collins: small lymphocyte B, lymphocytic-plasmacyic, small lymphocyte B, monocytoid

Working Formulation: (not specifically listed) SLL (some c/w CLL, some plasmacytoid); small cleaved or mixed small and large cell (follicular or diffuse)

Two tumors have been described in recent years, which have sufficient morphologic, immunophenotypic and clinical similarity to suggest that they may be related. These are the low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)

type [3, 4] and monocytoid B-cell lymphoma [5-8]. The nomenclature for these tumors has been confusing: some authorities have used the term monocytoid B-cell lymphoma for both nodal and extranodal disease [5, 6, 8], others have restricted monocytoid B-cell lymphoma to nodal disease [7], and it has not been clear what to call extranodal non-mucosa-associated tumors or nodal tumors with cells that are smaller than typical monocytoid B cells. The tumors show morphologic evidence of differentiation at least in part into cells of marginal zone type, which appear to have the capacity to mature into both monocytoid B cells and plasma cells, and appear to display tissue-specific homing patterns [9, 10]. It seems reasonable to postulate that the different clinical syndromes associated with tumors of this morphologic type may be a result of the homing pattern of the specific neoplastic clone [11-17]. In addition, proliferation of these cells at certain sites may depend on the presence of activated, antigen-driven T cells [18]. The term, marginal zone B-cell lymphoma, has been proposed to encompass tumors with these morphologic features, with modifiers to indicate the clinical subtype: extranodal or nodal.

Morphology (Table 3, Figures 5 and 6): Marginal zone B-cell lymphoma is characterized by **cellular heterogeneity, including marginal zone (centrocyte-like) cells (small, atypical cells resembling small cleaved follicular center cells or centrocytes, but with more abundant cytoplasm, similar to Peyer's patch, mesenteric nodal, or splenic marginal zone cells), monocytoid B cells, small lymphocytes, and plasma cells** (Figure 5A). Occasional large cells (centroblast- or immunoblast-like) are present in most cases. **Reactive follicles are usually present, with the neoplastic marginal zone or monocytoid B cells occupying the marginal zone and/or the interfollicular region** (Figure 5B); occasional follicles may contain an excess of marginal zone or monocytoid cells, giving them a neoplastic appearance (follicular colonization). In epithelial tissues, the marginal zone cells typically infiltrate the epithelium, forming so-called **lymphoepithelial lesions**. In lymph nodes they may have a perisinusoidal, parafollicular or marginal zone pattern of distribution (Figure 6). Plasma cells are often distributed in distinct subepithelial or interfollicular zones, and are neoplastic (monoclonal) in up to 40% of the cases.

Immunophenotype (Table 4): Tumor cells express SIg (M>G>A), lack IgD, and about **40% are CIg+**; B-cell-associated antigens (CD19, 20, 22, 79a) are expressed, and the tumors are **CD5-, CD10-**, CD23-, CD43-/+ CD11c +/-. Immunophenotyping studies are a useful adjunct to diagnosis, in excluding B-CLL (CD5+), mantle cell (CD5+) and follicle center (CD10+ CD43-, CD11c-, usually CIg-) lymphomas [19, 20].

Genetic Features: **No rearrangement of bcl-2 or bcl-1** is seen [21]; trisomy 3 and or t(11;18) have been reported in extranodal cases [22].

Clinical Features: There are two major clinical presentations of lymphoma with the above-described morphologic and immunologic features.

1. ***Extranodal marginal zone lymphoma (low-grade B-cell lymphoma of MALT type)***: These are tumors of adults, with a slight female predominance. Many patients have a history of autoimmune disease, such as Sjogren's syndrome or Hashimoto's thyroiditis, or of helicobacter gastritis. It has been suggested that "acquired MALT" secondary to autoimmune disease or infection in these sites may form the substrate for lymphoma development. The majority present with localized stage I or II extranodal disease, involving glandular epithelial tissues of various sites, most frequently the stomach; however, skin and soft tissues may be the presenting site as well [23-30]. The term, extranodal marginal zone lymphoma, can be used for cases not involving epithelial tissues. Dissemination occurs in up to 30% of the cases, often in other extranodal sites, with long disease-free intervals [30]. Localized tumors may be cured with local treatment [25, 26, 28]. Recent studies suggest that proliferation in some early MALT type tumors may be antigen-

driven [18], and that therapy directed at the antigen (helicobacter pylori in gastric lymphoma) may result in regression of early lesions [31]. When disseminated, they appear to be indolent and not curable. Transformation to large-cell lymphoma may occur.

2. ***Nodal Marginal Zone Lymphoma (provisional subtype)***: The majority of nodal monocytoid B-cell lymphomas occur in patients with Sjogren's syndrome or other extranodal MALT type lymphomas [6, 8], and therefore likely represent nodal spread of MALT type lymphoma. However, tumors with morphologic features identical to those described for extranodal MALT-type or monocytoid B-cell lymphomas have occasionally been reported with isolated or disseminated nodal involvement, in the absence of extranodal disease [5-8, 32]. Other sites involved include bone marrow and, rarely, peripheral blood [33]. The clinical course is indolent, and when disseminated, it is not usually curable with available therapy. Transformation to large-cell lymphoma may occur.

Postulated normal counterpart: Peripheral B cell with capacity to differentiate into marginal zone, monocytoid, and plasma cells.

B. Mantle Cell Lymphoma

Synonyms:

Rappaport: intermediately or poorly differentiated lymphocytic, diffuse or nodular (ILL/IDL/PDL)

Kiel: centrocytic (mantle cell) lymphoma

Lukes-Collins: small cleaved follicular center cell (FCC)

Working Formulation: small cleaved cell, diffuse or nodular; rarely diffuse mixed or large cleaved cell

Other: mantle zone lymphoma

Morphology (Table 3): This tumor is defined according to the Kiel classification criteria for centrocytic lymphoma [34-36]. In most cases the tumor is composed exclusively of **small to medium-sized lymphoid cells, usually slightly larger than normal lymphocytes, with more dispersed chromatin, scant pale cytoplasm and inconspicuous nucleoli** (Figure 3). In most cases, the nuclei are irregular or "cleaved," however, in some cases the cells are nearly round and in others they may be very small and resemble small lymphocytes. **Transformed cells with basophilic cytoplasm (centroblast-or immunoblast-like cells) are by definition extremely rare or absent.** A small proportion of the cases have larger nuclei with more dispersed chromatin, and a high proliferation fraction [20]. Because some of these resemble lymphoblastic lymphoma, the term "blastic" variant has been applied. The terms, "lymphoblastoid " or "blastoid" variant emphasize the cytologic resemblance to lymphoblasts, rather than to large transformed blasts (centroblasts or immunoblasts).

The pattern of mantle cell lymphoma is usually diffuse or vaguely nodular; well-defined follicles as in follicular lymphomas are rarely but occasionally seen. In many cases the tumor involves the mantle zones of at least some reactive follicles; less commonly, a pure mantle zone pattern occurs. Many cases contain individually scattered epithelioid histiocytes, creating a "starry-sky" appearance at low magnification.

Mantle cell lymphoma is a term proposed to replace centrocytic lymphoma, intermediate lymphocytic lymphoma (ILL), lymphocytic lymphoma of intermediate differentiation (IDL), and mantle zone lymphoma [36]. It corresponds to centrocytic lymphoma of the Kiel Classification, which is now believed not to arise from true germinal center centrocytes, but rather possibly from a subset of mantle zone B cells. In the original Working Formulation study, centrocytic lymphoma was included within the category of diffuse small cleaved cell lymphoma, and comprised the majority of the cases of this subtype. The blastoid variant and some other cases with larger cells may fall within the diffuse mixed or large cleaved cell categories of the Working Formulation [37]; however, the

tumor cells do not have basophilic cytoplasm and are distinct from the other lymphomas in these heterogeneous Working Formulation categories.

Immunophenotype (Table 4): The tumor cells are **SIgM+, usually IgD+, λ>κ, B-cell associated antigen+, CD5+**, CD10-/+, **CD23-**, CD43+, CD11c-. A prominent, disorganized meshwork of follicular dendritic cells (FDC) is present. Absence of CD23 is useful in distinguishing mantle cell lymphoma from B-CLL; CD5 is useful in distinction from follicle center and marginal zone lymphomas [20, 38].

Genetic features: A chromosomal translocation **t(11;14)** involves the Ig heavy chain locus and the bcl-1 locus on the long arm of chromosome 11 in the majority of the cases. This translocation results in overexpression of a gene known as PRAD1, which encodes for **cyclin D1**, a cell-cycle protein that is not normally expressed in lymphoid cells [39, 40]. A recently described antibody to Cyclin D1 detects the antigen in nuclei of virtually all mantle cell lymphomas and not in other typtes of low-grade B-cell lymphoma[41].

Clinical features: The tumor occurs in older adults, with a high male to female ratio; it is usually widespread at diagnosis. Sites involved include lymph nodes, spleen, Waldeyer's ring, bone marrow, blood, and extranodal sites, especially the gastrointestinal tract (lymphomatous polyposis) [42, 43]. The course is moderately aggressive, and it appears to be incurable with available treatment [44]. The median survival ranges from 3-5 years; the blastoid variant is more aggressive (median survival 3 years). Transformation to a large-cell lymphoma composed of centroblast and/or immunoblast-like cells does not appear to occur.

Postulated Normal counterpart: CD5+ CD23- peripheral B cell of inner follicle mantle.

C. B-Cell Chronic Lymphocytic Leukemia (B-CLL) / prolymphocytic leukemia (B-PLL) / Small lymphocytic lymphoma (B-SLL)

Synonyms:

Rappaport: well-differentiated lymphocytic, diffuse
Kiel: B-CLL, B-PLL; immunocytoma, lymphoplasmacytoid type
Lukes-Colins: small lymphocyte B, B-CLL
Working Formulation: small lymphocytic, consistent with CLL

Morphology (Table 3): Enlarged lymph nodes in patients with B-CLL show a characteristic infiltrate (Figure 2). The predominant cell is a **small lymphocyte, which may be slightly larger than a normal lymphocyte**, with clumped chromatin, usually a round nucleus, and occasionally a small nucleolus. **Larger lymphoid cells (prolymphocytes and para-immunoblasts) are always present, usually clustered in pseudofollicles (proliferation centers)**, imparting a pseudofollicular pattern, or less often, distributed evenly throughout the node [34]. Increased numbers of large cells may be associated with a more aggressive course [34, 45]. In some cases, the small lymphoid cells show moderate nuclear irregularity, which can lead to a differential diagnosis of mantle cell lymphoma (see below); if pseudofollicles and/or prolymphocytes and para-immunoblasts are present, a diagnosis of B-CLL should be made [36, 46].

Most patients whose lymph nodes contain the characteristic infiltrate associated with B-CLL will prove to have bone marrow and peripheral blood involvement at the time of the diagnosis or shortly thereafter; however some are non-leukemic at presentation and it is possible that some may not develop leukemia. The term small lymphocytic lymphoma has in the past been used to encompass not only the nodal counterpart of B-cell CLL, but also many MALT type lymphomas and probably also some T-cell neoplasms [20, 37]. The term small lymphocytic lymphoma should now be restricted to tumors that show the characteristic morphology and immunophenotype of B-CLL.

Some cases with the characteristic morphology and immunophenotype of B-CLL can have plasmacytoid differentiation, with cytoplasmic Ig and often a small M-component.

These cases correspond to the "lymphoplasmacytoid" immunocytoma of the Kiel Classification [35, 47]. The clinical course of these cases does not appear to differ markedly from B-CLL, and these tumors should be regarded as a variant of B-CLL.
Immunophenotype (Table 4) : The tumor cells of B-CLL have **faint SIgM**, are SIgD+/-, (CIg-/+), **B-cell-associated antigen+** (CD19, 20, 79a), **CD5+, CD23+** CD43+, CD11c-/+ (faint), and CD10- [20, 38, 48]. CD23 is useful in distinguishing B-CLL/SLL from mantle cell lymphoma. CD22 expression may be weak or undetectable, particularly by flow cytometry. Differences in antigen expression (such as CD11c) may be associated with variations in clinical course; further study of these variants is needed. Cases of B-PLL may be CD5-, have strong SIg, and more often express CD22 [49].
Genetics: Ig heavy and light chain genes are rearranged; trisomy 12 is reported in one-third of the cases, and abnormalities of 13q are seen in up to 25%. t(11;14) and bcl-1 rearrangement have been reported; these cases may need further study to rule out the possibility that they are examples of mantle cell lymphoma [50-52].
Clinical features: The majority of the cases occur in older adults; this disease comprise 90% of chronic lymphocytic leukemias in the U.S. and Europe. Most patients have bone marrow and peripheral blood involvement at diagnosis; tumor commonly involves multiple nodes, spleen, and liver; extranodal infiltrates may occur [37]. A small M-component may be found in some patients [47]. Occasional patients present with aleukemic nodal involvement, but most will ultimately be found to have or develop marrow and blood infiltration. The clinical course is indolent, and this disease is not usually considered curable with available therapy. Prolymphocytoid transformation or transformation to large cell lymphoma (Richter's Syndrome), may occur; these are usually diffuse large B-cell lymphomas, but cases resembling Hodgkin's disease have been reported.
Postulated Normal counterpart: Recirculating CD5+ CD23+ peripheral B cell [53].

D. Lymphoplasmacytoid Lymphoma / Immunocytoma

Synonyms:

Rappaport: well-differentiated lymphocytic, plasmacytoid; diffuse mixed lymphocytic and histiocytic
Kiel: immunocytoma, lymphoplasmacytic type
Lukes-Collins: plasmacytic- lymphocytic
Working Formulation: small lymphocytic, plasmacytoid; diffuse mixed small and large cell

Morphology (Table 3): The tumor consists of a diffuse proliferation of **small lymphocytes, plasmacytoid lymphocytes (cells with abundant basophilic cytoplasm, but lymphocyte-like nuclei), and plasma cells**, with or without Dutcher bodies, and by definition, **lacks features of B-CLL, mantle cell, follicle center cell, or marginal zone lymphomas.** The growth pattern is often interfollicular with sparing of the sinuses.

Many B-cell neoplasms may occasionally show maturation to plasmacytoid or plasma cells containing cytoplasmic immunoglobulin (CIg), including B-CLL, mantle cell, follicle center and marginal zone cell lymphomas. These cases should be classified according to their major features, and not as lymphoplasmacytoid lymphomas. There does appear to be a distinct disorder of small lymphoid cells that show maturation to plasma cells, without features of other lymphoma types, which corresponds to most cases of Waldenstrom's macroglobulinemia. These tumors usually lack CD5 and lack characteristic features of other lymphoma subtypes [20, 38, 48]. They correspond most closely to the lymphoplasmacytic immunocytoma of the Kiel classification [35, 47].
Immunophenotype (Table 4): The cells have surface and **cytoplasmic (some cells) Ig**, usually of IgM type, usually lack IgD, and are B-cell-associated antigens+ (CD19, 20,

22, 79a), **CD5-, CD10-**, CD43+/-; CD25 or CD11c may be faintly positive in some cases [20, 38, 47, 48]. Lack of CD5 and the presence of strong cytoplasmic Ig are useful in distinction from B-CLL.
Genetic features: Ig heavy and light chain genes are rearranged. No specific abnormality is known.
Clinical features: Lymphoplasmacytoid lymphoma/immunocytoma occurs in the same general age group as B-CLL. Sites involved include bone marrow, lymph nodes and spleen; less frequently peripheral blood or extranodal sites. The majority of patients have a monoclonal serum paraprotein of IgM type; hyperviscosity symptoms may occur (Waldenstrom's macroglobulinemia) [20, 35, 38, 47, 48]. (Note: other lympomas may also be associated with serum paraproteins.) The course is indolent and the disease is not generally curable with available treatment. Transformation to large-cell lymphoma may occur.
Postulated normal counterpart: CD5- peripheral B lymphocyte stimulated to differentiate to a plasma cell.

C. Follicle center lymphoma, follicular
Provisional cytologic grades: I (predominantly small cell), II (mixed small and large cell), III (predominantly large cell)
Synonyms:
Rappaport: nodular poorly differentiated lymphocytic (PDL), mixed lymphocytic-histiocytic, or histiocytic
Kiel: centroblastic/centrocytic follicular; follicular centroblastic
Lukes-Collins: small cleaved, large cleaved or large noncleaved FCC, follicular
Working Formulation: follicular, small cleaved, mixed, or large cell
Morphology (Table 3): This lymphoma is defined as a tumor **composed of follicle center cells, usually a mixture of centrocytes (cleaved follicle center cells) and centroblasts (large noncleaved follicle center cells). The pattern is at least partially follicular,** but diffuse areas may be present [34] (Figure 4). Sclerosis is common in diffuse areas. **Centrocytes typically predominate; centroblasts are usually in the minority, but by definition are always present.** Rare lymphomas with a follicular growth pattern consist almost entirely of centroblasts; since the follicular pattern implies a germinal center origin, we include these in the category of follicle center lymphoma.
Immunophenotype (Table 4): The tumor cells are usually SIg+ (IgM +/- IgD > IgG > IgA), B-cell associated antigen+, **CD10** +/-, **CD5-**, CD23-/+, **CD43-**, CD11c-. Tightly organized meshworks of FDC are present in follicular areas [20, 54, 55]. **BCL-2 protein expression is useful in distinguishing reactive from neoplastic follicles, since it is absent from reactive follicles and present in most follicular lymphomas** [56]; however this is not useful in distinguishing follicle center from other types of low-grade B-cell lymphoma, most of which also express BCL-2 protein. Lack of CD5 and CD43 is useful in distinguishing follicle center lymphoma from mantle cell lymphoma, and the presence of CD10 can be useful in distinguishing it from marginal zone cell lymphomas (see below).
Genetic features: **t(14;18)**, involving rearrangement of the bcl-2 gene, is present in 70-95% of the cases, resulting in expression of this "anti-apoptosis" gene, which is switched off at the translational level in normal germinal center cells; expression of the BCL-2 protein permits accumulation of long-lived centrocytes. This translocation occurs at an early stage of B-cell development, during immunoglobulin gene rearrangement [57], and occasional cells with rearranged bcl-2 genes can be detected in normal lymphoid tissues in some normal individuals [58]. These observations suggest that when a resting B cell that

carries the bcl-2 translocation undergoes blast transformation in response to antigen, failure to switch off the bcl-2 gene may contribute to development of a lymphoma.
Clinical features : Follicle center lymphoma affects predominantly adults, with an equal male:female incidence [37]. It constitutes as much as 40% of adult non-Hodgkin's lymphomas in the U.S.; the incidence is apparently lower elsewhere [35]. Most patients have widespread disease at diagnosis. Sites involved include predominantly lymph nodes, but also spleen, bone marrow, occasionally peripheral blood or extranodal sites. The clinical course is generally indolent, and it is not usually curable with available treatment. Both the number of centroblasts and the size of the centrocytes appear to correlate with prognosis [34, 59, 60]. Progression to diffuse large B-cell lymphoma may occur.
Postulated normal counterpart: Germinal center B cells, both centrocytes (small cleaved follicular center cells) and centroblasts (large noncleaved follicular center cells).

Differential diagnosis of low-grade gastric lymphomas:

1. Reactive/benign lymphoid infiltrate

Histologic and Immunohistologic features useful in differential diagnosis

Feature	MALT lymphoma	Mantle cell lymphoma	Follicular lymphoma	Gastritis
Follicles	Y	Y	Y	Y
Dense extrafollicular infiltrate	Y	Y	Y	N
Crypt abscesses	N/Y	N	N	Y
Extrafollicular small "cleaved" cells	Y	Y	N	N
Lymphoepithelial lesions	Y	N/Y	N/Y	N/RARE
Monotypic Ig: surface	Y	Y	Y	N
cytoplasmic	Y (40%)	N	N	N
Cyclin D1+	N	Y	N	N
Bcl2+ follicles	N	N	Y	N

Histological scoring for diagnosis of gastric MALT lymphoma (from Wotherspoon et al [31])

Grade	Description	Histological features
0	Normal	Scattered plasma cells in lamina propria. No lymphoid follicles
1	Chronic active gastritis	Small clusters of lymphocytes in lamina propria. No lymphoid follicles. No LELs
2	Chronic active gastritis with florid lymphoid follicle formation	Prominent lymphoid follicles with surrounding mantle zone and plasma cells. No LELs
3	Suspicious lymphoid infiltrate, probably reactive	Lymphoid follicles surrounded by small lymphocytes that infiltrate diffusely in lamina propria and occasionally into epithelium
4	Suspicious lymphoid infiltrate, probably lymphoma	Lymphoid follicles surrounded by marginal zone cells that infiltrate diffusely in lamina propria and into epithelium in small groups
5	Low-grade B-cell lymphoma of MALT	Presence of dense diffues infiltrate of marginal zone cells in lamina propria with prominent LELs

2. Distinguishing features of different types of low-grade B-cell lymphoma

MORPHOLOGIC FEATURES

LYMPHOMA TYPE	PATTERN	SMALL CELLS	LARGE CELLS
B-CLL/SLL	Diffuse with pseudofollicles	Round (may be cleaved)	Prolymphocytes Paraimmunoblasts
Lymphoplasmacytoid lymphoma	Diffuse	Round (may be cleaved) Plasma cells	Centroblasts Immunoblasts
Mantle cell lymphoma	Diffuse, vaguely nodular, mantle zone, rarely follicular	Cleaved (may be round or oval)	None
Follicle center lymphoma	Follicular +/- diffuse areas, rarely diffuse	Cleaved	Centroblasts
Marginal zone B-cell lymphoma	Diffuse, interfollicular, marginal zone, occasionally follicular (colonization)	Heterogeneous: round (small lymphocytes), cleaved (marginal zone/monocytoid B cells), plasma cells	Centroblasts Immunoblasts

IMMUNOHISTOLOGIC AND GENETIC FEATURES

LYMPHOMA TYPE	SIG	CIG	CD5	CD10	CD23	CD43	Cytogenetic abnormality	Oncogene rearranged
B-CLL/SLL	+[1]	-/+	+	-	+	+	trisomy 12 (30%)	NA
Lymphoplasmacytoid	+	+	-	-	-	-/+	NA	NA
Mantle cell	+	-	+	-/+	-	+	t(11;14)	bcl-1
Follicle center	+	-	-	+/-	-/+	-	t(14;18)	bcl-2
Marginal zone	+	+/-	-	-	-/+	-/+	trisomy 3	NA

+=90% positive; +/-= over 50% positive; -/+ less than 50% positive; -=< 10% positive (see text for abbreviations)

Approximate Frequency of Lymphoid Neoplasms in Adult Biopsy Specimens from Centers in the U.S. and Europe

	Lymph Node	Bone Marrow	Spleen	GI Tract	Skin
B-CELL NEOPLASMS: 86%	%	%	%	%	%
Indolent Neoplasms					
B-cell CLL/PLL/SLL	5-10	25-35	25-40	2	5-10
Lymphoplasmacytoid lymphoma/Immunocytoma	1-2	5-10	3	<1	1-3
Mantle cell lymphoma	2-6	1-3	1-5	2	<1
Follicle center lymphoma, follicular	25-40	10-15	20-25	5-10	10
Marginal zone B-cell lymphoma					
Extranodal (MALT type	1-5	<1	<1	20-50	5
Nodal	1-5	<1	<1	-	-
Splenic marginal zone lymphoma	-	<5	5-10	-	-
Hairy cell leukemia	<1	5-10	10-25	-	-
Plasmacytoma/plasma cell myeloma	<1	30-50	-	1	-
Aggressive Neoplasms					
Diffuse Large B-cell lymphoma	25-35	1	20	30	20
Burkitt's and Burkitt-like	1-2	<1	<1	1-2	<1
Precursor B-lymphoblastic leukemia/lymphoma	1-3	5-15	<1	<1	1-4
T/NK-CELL NEOPLASMS: 14%					
Indolent Neoplasms					
Mycosis fungoides/Sezary syndrome	1	-	-	-	25-30
Large granular lymphocyte leukemia (LGL)	<1	<1	<1	-	-
T-cell CLL/PLL	<1	<1	<1	<1	.5
Aggressive Neoplasms					
Peripheral T-cell lymphomas, unspecified	5-7	<1	<1	2-3	10-20
Angioimmunoblastic T-cell lymphoma (AILD)	1-4	<1	-	-	-
Angiocentric lymphoma	<1	-	-	-	<1
Intestinal T-cell lymphoma		-	-	1-5	-
Adult T-cell lymphoma/leukemia (ATL/L)	<1	<1	-	-	<1
Anaplastic large cell lymphoma (ALCL), CD30+	1-10	1-2	-	1-5	5-15
Precursor T-lymphoblastic lymphoma/leukemia	1-4	<1	<1	<1	<1

REFERENCES

1. Isaacson PG. Gastrointestinal lymphoma. Hum Pathol 1994; 25:1020.

2. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994; 84:1361.

3. Isaacson P, Wright D. Malignant lymphoma of mucosa associated lymphoid tissue. A distinctive B cell lymphoma. Cancer 1983; 52:1410.

4. Isaacson P, Spencer J. Malignant lymphoma of mucosa-associated lymphoid tissue. Histopathol 1987; 11:445.

5. Sheibani K, Burke J, Swartz W, Nademanee A, Winberg C. Monocytoid B cell lymphoma. Clinicopathologic study of 21 cases of a unique type of low grade lymphoma. Cancer 1988; 62:1531.

6. Ngan B-Y, Warnke R, Wilson M, Takagi K, Cleary M, Dorfman R. Monocytoid B-cell lymphoma: a study of 36 cases. Hum Pathol 1991; 22:409.

7. Nizze H, Cogliatti S, von Schilling C, Feller A, Lennert K. Monocytoid B-cell lymphoma: morphological variants and relationship to low-grade B-cell lymphoma of the mucosa-associated lymphoid tissue. Histopathology 1991; 18:403.

8. Shin S, Sheibani K, Fishleder A, et al. Monocytoid B-cell lymphoma in patients with Sjogren's syndrome: a clinicopathologic study of 13 patients. Hum Pathol 1991; 22:422.

9. Spencer J, Diss T, Isaacson P. A study of the properties of a low-grade mucosal B-cell lymphoma using a monoclonal antibody specific for the tumour immunoglobulin. J Path 1990; 160:231.

10. Smith-Ravin J, Spencer J, Beverley P, Isaacson P. Characterization of two monoclonal antibodies (UCL4D12 and UCL3D3) that discriminate between human mantle zone and marginal zone B cells. Clin exp Immunol 1990; 82:181.

11. Gowans J, Knight E. The route of recirculation of lymphocytes in the rat. Proc R Soc (Lond) B 1964; 159:257.

12. Gallatin W, Weissman I, Butcher E. A cell-surface molecule involved in organ-specific homing of lymphocytes. Nature 1983; 304:30.

13. Van den Oord J, De Wolf-Peeters C, De Vos R, Desmet V. Immature sinus histiocytosis. Light- and electron-microscopic features, immunologic phenotype, and relationship with marginal zone lymphocytes. Am J Pathol 1985; 1985:266.

14. Spencer J, Finn T, Pulford K, Mason D, Isaacson P. The human gut contains a novel population of B lymphocytes which resemble marginal zone cells. Clin Exp Immunol 1985; 62:607.

15. Van den Oord J, De Wolf-Peeters C, Desmet V. The marginal zone in the human reactive lymph node. Am J Clin Pathol 1986; 86:475.

16. Van den Oord J, De Wolf-Peeters C, Desmet V. Marginal zone lymphocytes in the lymph node. Hum Pathol 1989; 20:1225.

17. Butcher E. Cellular and molecular mechanisms that direct leukocyte traffic. Am J Pathol 1990; 136:3.

18. Hussell T, Isaacson P, Crabtree J, Spencer J. The response of cells from low-grade B-cell gastric lymphomas of mucosa-associated lymphoid tissue to Helicobacter pylori. Lancet 1993; 342:571.

19. Schmid C, Kirkham N, Diss T, Isaacson P. Splenic marginal zone cell lymphoma. Am J Surg Pathol 1992; 16:455.

20. Zukerberg L, Medeiros L, Ferry J, Harris N. Diffuse low-grade B-cell lymphomas: four clinically distinct subtypes defined by a combination of morphologic and immunophenotypic features. Am J Clin Pathol 1993; 100:373.

21. Pan L, Diss T, Cunningham D, Isaacson P. The bcl-2 gene in primary B-cell lymphomas of mucosa associated lymphoid tissue (MALT). Am J Pathol 1989; 135:7.

22. Finn T, Isaacson P, Wotherspoon A. Numerical abnormality of chromosomes 3, 7, 12, and 18 in low grade lymphomas of MALT-type and splenic marginal zone lymphomas detected by interphase cytogenetics on paraffin embedded tissue. J Pathol 1993; 170:335.

23. Hyjek E, Isaacson P. Primary B cell lymphoma of the thyroid and its relationship to Hashimoto's thyroiditis. Hum Pathol 1988; 19:1315.

24. Hyjek E, Smith W, Isaacson P. Primary B cell lymphoma of salivary gland and its relationship to myoepithelial sialadentiis (MESA). Hum Pathol 1988; 19:766.

25. Li G, Hansmann M, Zwingers T, Lennert K. Primary lymphomas of the lung: morphological, immunohistochemical and clinical features. Histopathology 1990; 16:519.

26. Medeiros L, Harmon D, Linggood R, Harris N. Immunohistologic features predict clinical behavior of orbital and conjunctival lymphoid infiltrates. Blood 1989; 74:2121.

27. Zukerberg L, Ferry J, Southern J, Harris N. Lymphoid infiltrates of the stomach: evaluation of histologic criteria for the diagnosis of low-grade gastric lymphoma on endoscopic biopsy specimens. Am J Surg Pathol 1990; 14:1087.

28. Cogliatti S, Schmid U, Schumacher U, et al. Primary B-cell gastric lymphoma: a clinicopathological study of 145 patients. Gastroenterology 1991; 101:1159.

29. Pelstring R, Essell J, Kurtin P, Banks P. Diversity of organ site involvement among malignant lymphomas of mucosa-associated tissues. Am J Clin Pathol 1991; 96:738.

30. Mattia A, Ferry J, Harris N. Breast lymphoma: a B-cell spectrum including the low grade B-cell lymphoma of mucosa associated lymphoid tissue. Am J Surg Pathol 1993; 17:574.

31. Wotherspoon A, Doglioni C, Diss T, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. Lancet 1993; 342:575.

32. Cogliatti S, Lennert K, Hansmann M, Zwingers T. Monocytoid B cell lymphoma: clinical and prognostic features of 21 patients. J Clin Pathol 1990; 43:619.

33. Carbone A, Gloghini A, Pinto A, Attadia V, Zagonel V, Volpe R. Monocytoid B-cell lymphoma with bone marrow and peripheral blood involvement at presentation. Am J Clin Pathol 1989; 92:228.

34. Lennert K. Malignant lymphomas other than Hodgkin's disease. . New York: Springer-Verlag, 1978.

35. Lennert K, Feller A. Histopathology of non-Hodgkin's lymphomas. (2 ed.). New York: Springer-Verlag, 1992.

36. Banks P, Chan J, Cleary M, et al. Mantle cell lymphoma: a proposal for unification of morphologic, immunologic, and molecular data. Am J Surg Pathol 1992; 16:637.

37. Non-Hodgkin's lymphoma pathologic classification project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a Working Formulation for clinical usage. Cancer 1982; 49:2112.

38. Stein H, Lennert K, Feller A, Mason D. Immunohistological analysis of human lymphoma: correlation of histological and immunological categories. Adv Cancer Res 1984; 42:67.

39. Rosenberg C, Wong E, Petty E, et al. Overexpression of PRAD1, a candidate BCL1 breakpoint region oncogene, in centrocytic lymphomas. Proc Natl Acad Sci USA 1991; 88:9638.

40. Williams M, Swerdlow S, Rosenberg C, Arnold A. Characterization of chromosome 11 translocation breakpoints at the bcl-1 and PRAD1 loci in centrocytic lymphoma. Cancer Res (Suppl) 1992; 52:5541.

41. Yang WI, Zukerberg LR, Mokotura I, Arnold A, Harris NL. BCL-1 (Cyclin D1) protein expression in low grade B-cell lymphomas and reactive hyperplasia. Am J Pathol 1994; (in press).

42. Isaacson P, MacLennan K, Subbuswamy S. Multiple lymphomatous polyposis of the gastrointestinal tract. Histopathology 1984; 8:641.

43. O'Briain D, Kennedy M, Daly P, et al. Multiple lymphomatous polyposis of the gastrointestinal tract: a clinicopathologically distinctive form of non-Hodgkin's lymphoma of centrocytic type. Am J Surg Pathol 1989; 13:691.

44. Meusers P, Engelhard M, Bartels H, et al. Multicentre randomized therapeutic trial for advanced centrocytic lymphoma: anthracycline does not improve the prognosis. Hematol Oncol 1989; 7:365.

45. Ben-Ezra J, Burke J, Swartz W, et al. Small lymphocytic lymphoma: a clinicopathologic analysis of 268 cases. Blood 1989; 73:579.

46. Perry D, Bast M, Armitage J, Weisenburger D. Diffuse intermediate lymphocytic lymphoma: a clinicopathologic study and comparison with small lymphocytic lymphoma and diffuse small cleaved cell lymphoma. Cancer 1990; 66:1995.

47. Lennert K, Tamm I, Wacker H-H. Histopathology and immunocytochemistry of lymph node biopsies in chronic lymphocytic leukemia and immunocytoma. Leuk Lymphoma 1991; (Suppl):157.

48. Harris N, Bhan A. B-cell neoplasms of the lymphocytic, lymphoplasmacytoid, and plasma cell types: immunohistologic analysis and clinical correlation. Hum Pathol 1985; 16:829.

49. Bennett J, Catovsky D, Daniel M-T, et al. Proposals for the classification of chronic (mature) B and T lymphoid leukemias. J Clin Pathol 1989; 42:567.

50. Athan E, Foitl D, Knowles D. Bcl-1 rearrangement: frequency and clinical significance among B cell chronic lymphocytic leukemias and non-Hodgkin's lymphomas. Am J Pathol 1991; 138:591.

51. Croce C, Tsujimoto Y, Erikson J, Nowell P. Chromosome translocations and B cell neoplasia. Lab Invest 1984; 51:258.

52. Tsujimoto Y, Yunis J, Onorato-Showe L, Erikson J, Nowell P Croce, CM. Molecular cloning of the chromosomal breakpoint of B-cell lymphomas and leukemias with the t(11;14) chromosome translation. Science 1984; 224:14.

53. Kipps T. The CD5 B cell. Adv Immunol 1989; 47:117.

54. Harris N, Nadler L, Bhan A. Immunohistologic characterization of two malignant lymphomas of germinal center type (centroblastic/centrocytic andf centrocytic) with monoclonal antibodies: follicular and diffuse lymphomas of small cleaved cell types are related but distinct entities. Am J Pathol 1984; 117:262.

55. Stein H, Lennert K, Feller A, Mason D. Immunological analysis of tissue sections in diagnosis of lymphoma. In: Hoffbrand A ed. Recent Advances in Haematology. New York: Churchill Livingstone, 1985. 11: 127.

56. Pezzella F, Tse A, Cordell J, Pulford K, Gatter K, Mason D. Expression of the Bcl-2 oncogene protein is not specific for the 14-18 chromosomal translocation. Am J Pathol 1990; 137:225.

57. Tsujimoto T, Cossman J, Jaffe E, Croce C. Involvement of the bcl-2 gene in human follicular lymphoma. Science 1985; 288:1440.

58. Limpens J, de Jong D, van Krieken J, et al. Bcl-2 in benign lymphoid tissue with follicular hyperplasia. Oncogene 1991; 6:2271.

59. Mann R, Berard C. Criteria for the cytologic subclassification of follicular lymphomas: a proposed alternative method. Hematological Oncology 1982; 1:187.

60. Nathwani B, Metter G, Miller T, et al. What should be the morphologic criteria for the subdivision of follicular lymphomas? Blood 1986; 68:837.