

Chapter 5

The Endoscopic Biopsy: How to Proceed and How to Look at a Biopsy



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Abstract Pathology is one of the tools for reaching a diagnosis. Like all procedures in medicine, the analysis of biopsies has some limitations. The diagnostic yield can be increased by using good quality samples, by optimizing the number of samples and sections, by optimal preparation of the samples and by confronting the findings with appropriate clinical information. Numbers of samples needed depend on the indication for the endoscopic procedures. When reading a biopsy, analysis can be improved with a systematic approach. This implies a proper knowledge of the normal histology and of potential artifacts. The pathologists should take note of the origin, the number, and the size of the samples and subsequently evaluate the architecture and cytological aspects of the specimen. The analysis can be improved by using a checklist or pro forma report.

Keywords Endoscopic biopsy · Diagnostic yield · Sampling · Sampling error · Diagnostic accuracy · Orientation · Optimal number of biopsies · Number of biopsies · Origin of biopsies · Size of biopsies · Architecture · Sensitivity · Specificity · Artifact · Bowel preparation · Pseudolipomatosis · Barium

In routine clinical practice, endoscopic biopsies are obtained for diagnostic purposes and during a follow-up of the patient. Follow-up biopsies are used for confirmation of a diagnosis, for assessment of disease activity and for cancer surveillance or identification of complications. Optimally, the pathologist should be aware of the precise goal of the biopsy.

The diagnostic yield of histopathology depends upon the experience of the pathologist and on the quality of the biopsy samples and is influenced by sampling errors. Diagnostic accuracy increases when biopsy samples are analyzed by expert

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pathologists and by training non-expert general pathologists although the quality of the samples may be more important [1, 2]. The quality of the samples is influenced by a variety of elements such as the size and shape of the biopsy forceps, the nature and location of the disease, the experience of the endoscopist and the number of samples. Samples are usually obtained with pinch biopsy forceps. Currently a wide variety of single-use and reusable instruments are available. Disposable instruments may be superior probably because the forceps are sharper [3]. A distinction can be made between those with oval or elongated and those with round cups. Generally the samples obtained with oval elongated cups are deeper and those with oval fenestrated cups are larger. A forceps with round cups may be more appropriate for children in order to avoid complications. The size of the biopsy forceps determines partly the size (surface and depth) of the samples. The small forceps has a width of 1.8 mm when opened. The average forceps has a 2.4–2.8 mm diameter and allows to obtain samples containing the muscularis mucosae (and upper submucosa) in 60% of the cases. Therefore endoscopic biopsies are not so appropriate for a diagnosis of vasculitis or amyloidosis, because arteries and veins are mainly located in the submucosa. The larger Jumbo forceps has a 3.4 mm diameter. Samples obtained with this forceps are larger, but they usually contain not more submucosa, and the risk of complications (perforation and bleeding) may be more important, whereas it is minimal with the smaller forceps (if the patient has normal coagulation). A forceps can have a central spike for improved anchorage, so that it stays in position in the mucosa, during the procedure. The spike can induce artifacts which should not be confused with erosions. Colitis can be a diffuse process, a more right-sided process or a discontinuous disease. This is not only important for Crohn's disease but also for a diagnosis of collagenous or lymphocytic colitis. Thickening of the subepithelial collagen table in collagenous colitis is indeed not homogeneous. It is therefore important to have biopsies from the different areas of the colon associated with biopsies from the terminal ileum because the location of lesions can help for the diagnosis. This implies that several biopsies are obtained, ideally from diseased and healthy areas (if present), and that the biopsy specimens from different segments are presented in different containers to the pathology lab. Random samples from the same area can be in a single container. The lesions which are biopsied may be important. Indeed, according to some studies, biopsies of aphthoid ulcers more commonly show granulomas, which are diagnostic for Crohn's disease. Sampling should include also normal mucosa because this may reveal also significant features [4]. ECCO (European Crohn's and Colitis Organisation) recommendation published concerning sampling states that at the onset of the disease or during the first examination, "For a reliable diagnosis of inflammatory bowel disease (IBD), ileocoloscopy rather than rectoscopy should be performed. A minimum of two biopsies from at least five sites along the colon, including the rectum, and the terminal ileum should be obtained." In patients with fulminant colitis, two samples from at least one site, preferentially the rectum should be obtained because of the risks inherent to the procedure [5].

During follow-up of patients with colitis, a smaller number of biopsy samples may confirm the diagnosis and give information regarding disease activity. When the goal of the biopsy is confirmation of the diagnosis, it is appropriate to review the

original set of biopsies. Furthermore, it is important to take into account the treatment given to the patient and the duration of the disease. In postsurgical follow-up of patients with Crohn's disease, biopsies of the neo-terminal ileum are indicated when disease recurrence is suspected. Where patients have undergone ileal pouch-anal anastomosis, biopsies of the afferent limb are useful when Crohn's disease is suspected. Multiple biopsies are indicated when the patient is investigated during screening for dysplasia (=intraepithelial neoplasia). Crohn's disease and ulcerative colitis carry an increased cancer risk. A pathway of "colitis-dysplasia cancer" has been identified, and this allows surveillance of patients with an increased risk (long-standing disease, extensive colitis, ulcerative colitis with primary sclerosing cholangitis, persistent microscopic disease activity, family history, etc.). It has been estimated that 33–64 biopsies are required to detect dysplasia with 90% and 95% probabilities, respectively. Yet, with 20–40 biopsies, less than 0.1% of the colorectal mucosa is covered [6, 7]. Current practice guidelines recommend to take four biopsy specimens from every 10 cm (0.05% of the entire area of the colon) of diseased bowel in addition to macroscopically atypical lesions [8]. However, the detection rate of IBD-related dysplasia can substantially be improved with targeted biopsies obtained with the newly developed endoscopic techniques such as magnifying colonoscopy, and this procedure should replace the random biopsy guidelines in the future because overall the diagnostic yield of random biopsies is poor [5]. Training of endoscopists is also an important issue. In the literature, there are guidelines for numbers and site of biopsies for the most common conditions. This is however not so for all diseases that can affect the colon. In general, when no guidelines are available, it seems appropriate to take biopsies from lesions but also from noninvolved areas and from the terminal ileum and to submit these samples to the laboratory in separate containers with an indication of the site of origin.

Proceeding Biopsy

All tissue samples should be fixed immediately by immersion in buffered formalin or an equivalent solution prior to transport to the laboratory of pathology. Orientation of the samples using filter paper (submucosal side down) before fixation may yield better results, because it allows perpendicular sections and thus a better assessment of architectural abnormalities. Without previous orientation, sections can be transverse which is more difficult for the assessment of the architecture and the distribution of the lamina propria cellular infiltrate. Some laboratory use inclusion in agar to appropriately orientate the biopsies. The ideal number of biopsy sections which should be examined in routine practice has not been established. Numbers vary between two and six in different studies [9, 10]. The diagnostic yield increases though when more sections are examined. It is not clear whether serial sections or step sections from different levels of the sample should be examined. In one comparative study of rectal biopsies, serial sectioning increased the ability to detect focal abnormalities including granulomas compared to step sectioning [11]. In routine practice, step sections may be the

most simple procedure. It has been proposed to obtain two to three tissue levels, each consisting of five or more sections. Routine staining with hematoxylin and eosin is appropriate for diagnosis. Special stains, such as immune histochemistry or other techniques for diagnostic purposes, are not needed routinely. They can eventually be helpful though for the assessment of CD3-positive T lymphocytes (in lymphocytic colitis) or the presence of collagen or tenascin (in collagenous colitis) or for the search of granulomas, using antibodies directed against CD68.

The biopsy samples should be accompanied by clinical information including endoscopic findings as well as the age of the patient, duration of disease, duration and type of treatment, immune status, comorbidity, and travel history [5].

How to Look at a Biopsy

The purpose of the microscopic examination should be to reach a level of diagnosis that allows identification of the etiology of the symptoms or the disease for which the endoscopy is performed. This implies usually that the pathologist has access to the clinical history, information regarding the bowel preparation and over-the-counter or prescription drug history [4]. Microscopic analysis should however start without looking at this information. The pathologist needs to form a personal opinion. He should look first at the number, size, and origin of the samples. This defines the limits of the analysis. When only one sample without submucosa is present, the reliability of the diagnosis may be questionable.

The mucosa with the muscularis mucosae and the upper part of the submucosa should be available for a correct histological examination. Table 5.1 shows the dif-

Table 5.1 How to look systematically a biopsy

Low magnification
Number of biopsies
Homogenous or heterogenous features
Architecture of the mucosa: irregular surface or not, villous aspect or not
High magnification
Surface: necrotic debris, abundant mucus, pathogens, crystals, etc.
Epithelial cells: columnar, vacuolization, flattening, mucin depletion, apoptotic bodies, intraepithelial lymphocytosis, detachment from subepithelial band, etc.
Collagen band: normal, increased thickness, irregular-jagged aspect
Crypt architecture: parallel, branching, atrophic, degenerative, serrated, dilated, crypt abscess, dysplastic epithelium
Paneth cells: present or not
Density, distribution and composition of the lamina propria cellular infiltrate: active or chronic inflammatory cells, superficial, patchy, focal, or diffuse infiltrate matrix of the lamina propria: presence of fibrosis, congestion, hyalinization, muscle fibers, granulation tissue
Specific features: granulomas, microorganisms
Components of the submucosa: vessels, ganglia of the submucosal plexus, etc.

ferent steps on how to look a biopsy. The biopsies should be evaluated first at low magnification. At low magnification, it is already possible to see if all specimens are affected by a disease process or not. This will provide an idea of diffuse or discontinuous disease.

Multiple samples from different sites can already provide some clues for a diagnosis. Right-sided colitis is more common in Crohn's disease and less usual in ulcerative colitis, unless the patient has been treated with local therapy such as enemas. Sadly, in routine practice, the pathologist has often only biopsies from inflamed areas. Diverticular disease-associated colitis should be considered when biopsies from the sigmoid are involved, whereas samples from the rectum and right colon are normal. If only biopsies from the inflamed sigmoid are available, it may be impossible to provide a final diagnosis. Samples could be signed as "inflammatory bowel disease-like features," but diverticular colitis must be considered in the differential diagnosis, especially when the patient is middle aged. Diversion colitis is likely when samples from an excluded rectum are abnormal, whereas samples from the colon in transit are normal. For this diagnosis, minimal knowledge of the clinical situation is imperative.

Subsequently, the architecture of the mucosa of the different samples should be assessed. It has been shown that architectural changes can be observed with good reproducibility and that they have good sensitivity and specificity for a diagnosis of IBD [12]. There are however some anatomic variations [3]. Abnormalities in the rectum alone are less useful as they might be a variant of normality. In the rectum, the crypts are usually widely spaced.

Subsequently the biopsies should be evaluated at higher magnification in a systematic fashion including (a) mucosal surface and villous architecture, (b) crypt epithelium, (c) lamina propria constituents, (d) specific features (granuloma, pseudomembrane, etc.) and (e) submucosal structures.

It is important to examine the surface of the specimen and to look for the presence of any abnormality which can include necrotic debris, abundant mucus and pathogens such as spirochetes, cryptosporidia, amoebae, or crystals such as in Kayexalate- and sevelamer-induced colitis [13–15].

Spirochetosis, for instance, is characterized by the presence of a thin, carpet-like layer of spirochetes attached on the colorectal surface epithelium, forming a "bluish" false brush border (Fig. 5.1). The major species is *Brachyspira aalborgi*. Infection is usually asymptomatic and not associated with active inflammation or mucosal injury [16]. *Entamoeba histolytica* infection can be recognized by the presence of trophozoites on the surface (Fig. 5.2). They should not be confounded with desquamated goblet cells. Kayexalate crystals have narrow, rectangular "fish scales" and are violet on routine staining and magenta on periodic acid-Schiff with diastase (Fig. 5.3). Sevelamer crystals (Renagel and Renvela, Genzyme; phosphate-lowering agents) appear as broad, curved, and irregularly spaced "fish scales" with a variably eosinophilic to rusty brown color on hematoxylin and eosin staining. Periodic acid-Schiff-alcian with diastase staining shows a violet color. Both products can be used in patients with chronic kidney disease. Cholestyramine has to be considered in the differential diagnosis. This compound

Fig. 5.1 Microphotograph showing a bluish aspect covering the surface indicating the presence of spirochetes forming a false brush border ($\times 40$)

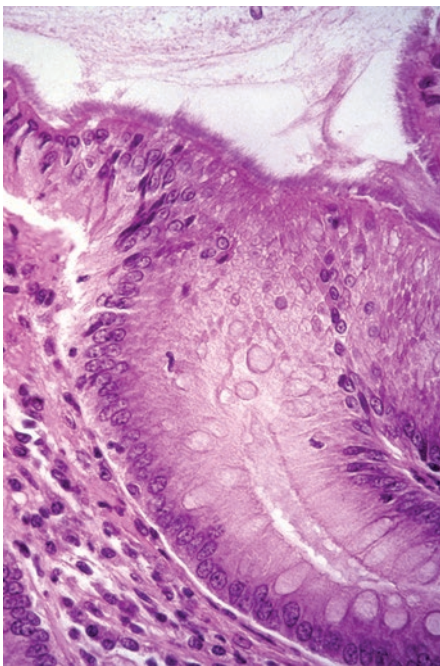
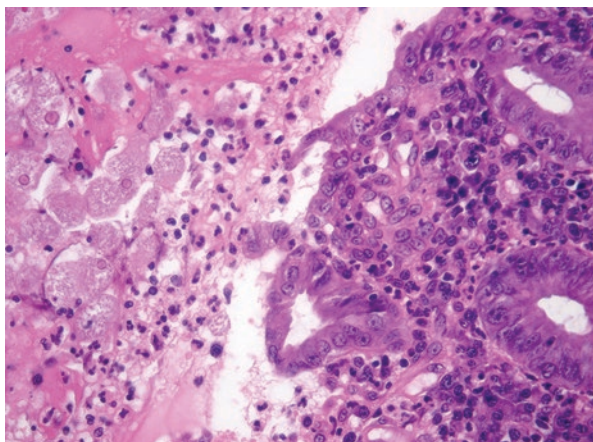


Fig. 5.2 Microphotograph showing the presence of numerous trophozoites of entamoeba covering the surface of the biopsy ($\times 40$)



lacks internal “fish scales,” is bright orange on routine staining and variably gray or hot pink on periodic acid-Schiff with diastase, and is unassociated with mucosal injury [17].

The surface architecture is also an important diagnostic feature. The normal colonic surface is flat; an irregular surface can be observed in some types of colitis. An irregular, villiform surface is the result of the widening of the crypts giving the mucosal surface a fingerlike appearance (Fig. 5.4).

Fig. 5.3 Microphotograph showing the presence of crystals on the surface suggestive of Kayexalate ($\times 40$)

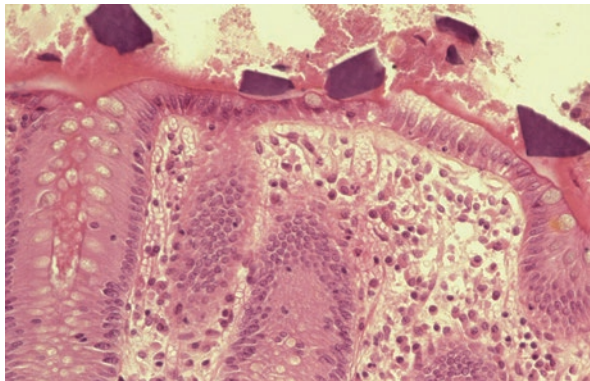
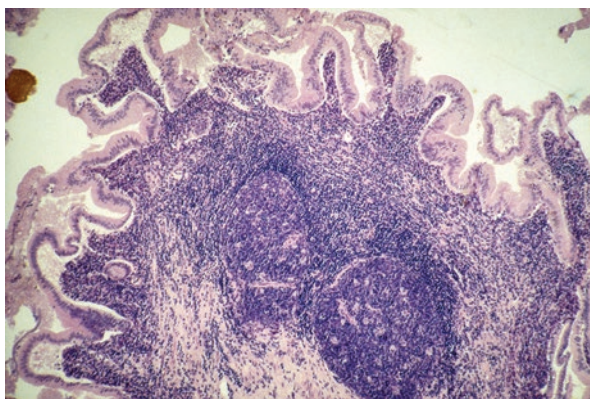


Fig. 5.4 Microphotograph showing an irregular, villiform surface which can be observed in ulcerative colitis ($\times 10$)



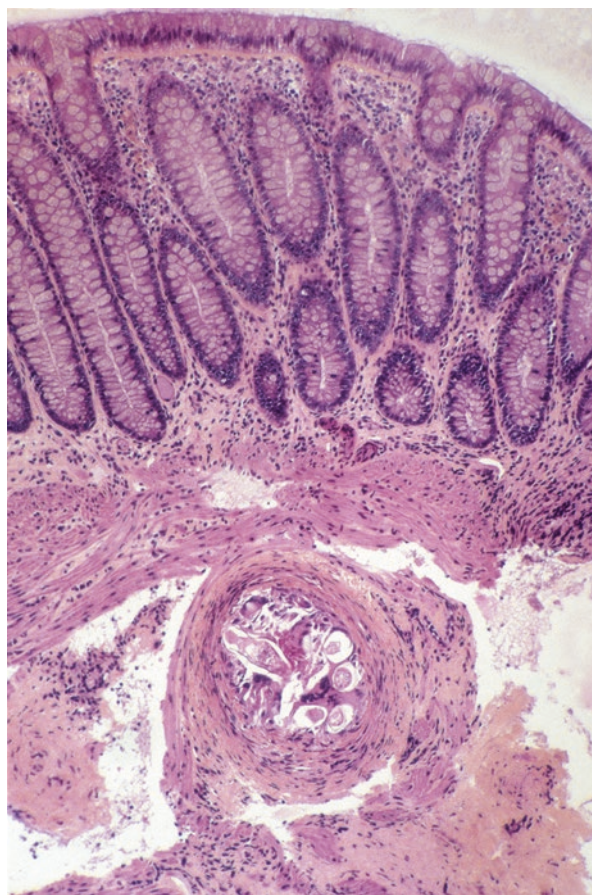
The next step is to look at the cytology of surface and crypt epithelial cells to see if they are highly columnar and well differentiated or not. Degeneration of the surface epithelium without accompanying inflammation is uncommon. It may be the result of poor tissue fixation or an intensive bowel preparation or repetitive damage in motility disorders. Apoptotic bodies may be visible. They are markers of increased epithelial cell destruction (viral infection, various luminal influences, surfactant loss, etc.).

Simultaneously the distribution, the density, and the composition of the lamina propria cellular infiltrate and the aspect of the stroma are examined. The distribution of the inflammation is another feature that can be assessed with good reproducibility [12].

Finally, the direct identification of specific features such as granulomas and pseudomembranes and the owl's eye inclusion or protozoal infection can orientate toward a precise diagnosis (Fig. 5.5).

The pathologist should look for the presence of blood vessels in the submucosa and, if present, for the presence of signs of vasculitis or amyloid and examine also the appearance of the ganglia of the submucosal plexus.

Fig. 5.5 Microphotograph showing shistosoma granulomas with concentric fibrosis and giant cells ($\times 10$)



Abnormalities should be noted, and a preliminary diagnosis should be made, which is then confronted with the available clinical data, such as the disease duration, the treatment received and the endoscopic findings, the immune status, and the age of the patient. The density of the lamina propria cellular infiltrate may indeed differ according to the immune status of the patient. In transplant patients, patients with human immunodeficiency virus (HIV) infection and patients receiving immune suppression, the inflammatory cell infiltrate may be less prominent. After careful analysis, the findings can be matched with the patient's age and history. The age of the patient may point to some diseases such as diverticular-associated colitis and ischemic colitis which are more common in middle-aged or elderly patients. The presentation of inflammatory bowel diseases may be less characteristic in pediatric patients [5]. Overall analysis of biopsies could be improved by using a checklist for the different items (see Table 5.1). In some types of colitis, these items could (or should?) be scored (see Chap. 18).

Artifacts

Very often endoscopic biopsies show some squeeze artifact in the deeper part and partial or complete absence of surface epithelial cells. The latter is usually the result of the biopsy procedure. The artifactual nature of the surface damage can be established by searching for remnant epithelial cells. These are usually well differentiated and highly columnar. When epithelial damage is genuine, remnant epithelial cells appear attenuated and have a darkly staining cytoplasm. This is however more difficult when the mucosa is already damaged by the disease. It may indeed be difficult to distinguish a genuine erosion and loss of surface epithelial cells from artifact-induced damage in samples from severe ileocolitis.

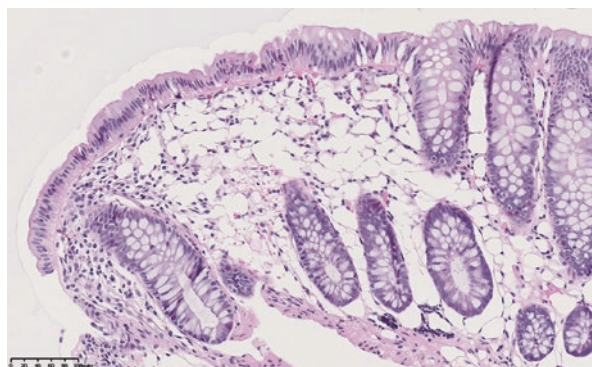
A well-oriented specimen is essential for optimal evaluation. Incorrect tissue orientation and tangential sectioning may cause misdiagnosis. Difficulties with proper tissue orientation are most common with endoscopical biopsies given their smaller size. Evaluation of colonic crypt architecture, height of the villus, and thickness and regularity of the subepithelial band may be hindered significantly by tangential sectioning.

Endoscopical electrocautery snare frequently results in thermodesiccation of the tissue, compressing crypts together and altering the nuclear features which are frequently distorted, pyknotic, and elongated. Crush or compression artifacts can occur with endoscopic forceps resulting in a condensation of the lymphoplasmacytic component that can be misinterpreted as chronic inflammation.

Absence of muscularis mucosae can result in colonic crypts or villi becoming shorter and widely spaced.

Diagnostic accuracy of colonoscopy depends on the quality of colonic cleansing. Bowel preparation includes diet, enemas, high-volume gut lavage, and rectal irrigation [18]. In some occasions, adjuncts are used to improve the results. Currently, preparation is mainly based on oral aqueous sodium phosphate (NaP) solutions and tablets, and polyethylene glycol (PEG) solutions, especially low-volume solutions. These are well tolerated by the majority of the patients [19]. PEG does not alter the histology or at least, the changes are less prominent than with NaP. Endoscopic and histological abnormalities have been reported with NaP and other compounds. A pattern of acute colitis with basal cryptitis and focal colitis have been described following bowel preparation with oral sodium phosphate and bisphosphonate enemas mimicking a nonsteroidal anti-inflammatory drug-induced injury or an inflammatory bowel disease ([20]; see also drug-induced colitis). Hyperosmotic or hypertonic enemas may cause sloughing of surface epithelium up to the point that the epithelial cells are completely stripped away. Superficial cells are replaced by young, attenuated cells, migrating from the crypts. Increased apoptosis has also been noted. As a result of cell loss, increased cell proliferation determined by mitotic counts and immune histochemistry with antibodies against proliferation markers is observed [21]. Neutrophils can be present in the lamina propria. The edematous lamina propria may contain extravasated red blood cells, some of which may be

Fig. 5.6 Microphotograph showing pseudolipomatosis ($\times 10$)



lyzed. Mucin release may be prominent. Bisacodyl, a poorly absorbed diphenylmethane that stimulates colonic peristalsis, can be used as an adjunct with PEG or NaP. It may be associated with edema and the appearance of occasional neutrophils beneath the surface epithelium, particularly when administered in the rectum. The changes usually resolve within a week.

Insufflation of air during the endoscopic procedure may induce “pseudolipomatosis” or “mucosal pneumatosis.” This is due to small trauma present before or induced by the friction of the instrument against the mucosa. The air used to dilate the lumen and visualize the mucosa may infiltrate the tissue and cause small, clear, bubble-like spaces which resemble adipocytes (Fig. 5.6). This has no clinical implications [22]. Pseudolipomatosis has also been linked to disinfection of the instrument with peroxide agents (peracetic acid or hydrogen peroxide) [23].

In the past glutaraldehyde has been used for disinfection of endoscopes. This practice has been found to be responsible for acute self-limited chemical colitis appearing within 48 h of colonoscopy or sigmoidoscopy. The morphological features may mimic ischemia [24]. Colonic biopsies reveal vascular congestion, crypt damage and an increase in the number of foamy macrophages. Lesions may already appear in biopsies obtained during withdrawal of the endoscope. This method of disinfection should not be used anymore nowadays.

Contrast media such as barium sulfate, an inert water-insoluble metallic element used for various radiographic studies, can induce a variety of rare complications including perforation with peritonitis, granuloma formation, ischemic necrosis, “barium” appendicitis and bezoar or mass formation with subsequent obstruction and/or mucosal injury.

Barium is manufactured with properties to make it more adherent to mucosal surfaces. This adherence leads to clumps which are usually recognizable as whitish crystalline material in aggregates on the surface and occasionally in the mucosa or submucosa. Iodinated contrast media can be responsible for diarrhea because of the osmolarity of the product. They have been associated in rare instances with necrosis of the bowel wall in infants and with cecal perforation in adults. A possible mechanism is a large shift of fluid into the intestine because of the hypertonic nature of the substances. Fragments of

crospovidine, a pharmaceutical filler can occasionally be recovered, also in biopsy samples from inflamed areas but these are probably not related to the inflammation. In general however, the pathologist has to give attention to material not included in the tissue because this may be relevant.

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