American Society of Clinical Oncology/College of American Pathologists Guidelines Should Be Scientifically Validated

To the Editor.—Although I agree with the majority of the “American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer” by Wolff et al., I am concerned with the sample exclusion criteria for human epidermal growth factor receptor 2 (HER2) immunohistochemistry (Table 5, p 27), both as they relate to the issue at hand and for the precedent this list of guidelines sets in an area of pathology certain to see more regulation.

The American Society of Clinical Oncology/College of American Pathologists panel delineated optimal formalin fixation time for HER2 immunohistochemistry performed on excisional biopsies as 6 to 48 hours. Furthermore, the panel mandates that a negative HER2 result from suboptimal specimens (ie, those fixed less than 6 hours or longer than 48 hours) be qualified in the report. It is intuitive that grossly underfixed specimens (ie, those fixed less than 6 hours or longer than 48 hours) should be qualified in the report. A recent review by Goldstein et al.1 entitled “Recommendations for Improved Standardization of Immunohistochemistry,” suggests a minimum formalin fixation time of 8 hours (recommendation 1). No maximum fixation time is recommended, and it is stated that “in general, underfixation is a substantially larger problem than over-fixation.”1 (p126)

Reading the ARCHIVES article in question I failed to discover any referenced study supporting the sample exclusion criteria. The authors simply allude to previous consensus conferences dealing with HER2 testing (Appendix E). Subsequently, Patrick Fitzgibbons, MD, an author of the guideline article1 and chair of the College of American Pathologists Immunohistochemistry Committee, acknowledged to me in an e-mail (March 2007) that studies confirming the hour-by-hour impact of formalin fixation on HER2 testing over the range of fixation intervals seen in clinical practice have not been completed. It is axiomatic that promulgated guidelines should be evidence based and scientifically validated. In the absence of peer-reviewed study in its support, adoption of the greater than 48-hour formalin fixation exclusion criterion would be counterproductive. This is especially true in light of the potential impact of said criterion on current laboratory practice (ie, necessitating staffing histology on the weekend to accommodate Friday morning breast cancer surgeries). Based on the evidence cited herein, a 72-hour maximum fixation exclusion criterion would be more appropriate, allowing for routine weekend fixation while enabling accurate and reproducible HER2 testing.

James F. Lombardo, MD
Ogden Regional Medical Center
Ogden, UT 84405

In Reply.—The American Society of Clinical Oncology/College of American Pathologists panel appreciates thoughtful commentary that has been provided to us by personal communication to various members as well as to the College of American Pathologists or as letters to the editor of Archives of Pathology & Laboratory Medicine or CAP Today. These thoughtful efforts help us to review problematic issues so that future revisions can address them.

To date, most concerns relate to specimen handling and its effect on human epidermal growth factor receptor 2 (HER2) test results. Understandably, there is consternation expressed about the lack of scientific evidence related to fixation types and fixation times. We share that consternation. The panel reviewed existing scant information and depended also on the extensive experience of many of the panel members and experts from large commercial laboratories who provided us with their input. All guidelines created by the American Society of Clinical Oncology or the College of American Pathologists in the past have depended on both scientific evidence and expert opinion, especially when existing evidence was scanty or nonexistent.


The author has no relevant financial interest in the products or companies described in this article.

This letter has been jointly published by consent in the ARCHIVES and CAP Today.
It was the considered and unanimous opinion of panel experts that defining the guideline fixative should be based on the requirements of the existing Food and Drug Administration–approved testing methods for HER2. All of those methods specify that tissue must be fixed in buffered formalin, although the length of fixation time is not described. The panel and these experts also felt strongly that the guideline needed to define standardized fixation intervals and then modify those requirements if necessary when and if data about optimal intervals became available. The expert panel members felt that intervals of 6 to 48 hours were most commonly recommended for breast cancer predictive tests. I presented published data from Intermountain Healthcare, which clearly demonstrated the adverse impact of prolonged fixation on estrogen receptor results in our health care system. Because breast specimens are submitted for estrogen receptor assays as well as for HER2 assays, these intervals seemed the most appropriate recommendation at this time. The adverse effects of underfixation are well known, as is pointed out by the letter writer and documented in the literature. It is likely that the recommendation for fixation of core biopsies will also be revised in the future to a minimum of 6 hours, based on recent published work. We look forward to other data validating or suggesting modification of fixation intervals during the next year. The panel is committed to modifying the document as needed based on input from the pathology and oncology community.

Our recommendation to provide information in any negative HER2 report about the potential impact of prolonged or foreshortened fixation time was included to guide oncologists in clinical decisions. Oncologists usually assume that any test result is accurate. Providing information about mitigating circumstances will help them to understand the complexities of these test interpretations so that they can make better informed decisions for their patients. The intent of all pathologists and oncologists is to provide the most appropriate treatment to patients based on accurate testing data. It is fervently hoped that the current guideline will provide us with strategies to make such accurate testing more widespread. The panel is committed to changing the guideline when and if data are provided to recommend those changes.

M. ELIZABETH H. HAMMOND, MD
Co-Chair, ASCO/CAP HER2 Guideline Panel
Intermountain Healthcare
LDS Hospital
Department of Pathology
Salt Lake City, UT 84143

ON BEHALF OF THE ASCO/CAP PANEL ON HER-2 TESTING IN BREAST CANCER

Malakoplakia Outside the Urinary Tract

To the Editor.—I read with great interest the comprehensive review of malakoplakia outside the urinary tract by Drs Yousef and Naghibi1 in the February 2007 issue of the Archives of Pathology & Laboratory Medicine and wish to complement their review by reporting a case of malakoplakia occurring in Barrett esophagus, a site and an associated condition that are yet to be reported.

A 93-year-old man presented with anemia and a 1-week history of weakness and melena. An upper gastrointestinal endoscopy revealed small gastric ulcers and a 2 × 1.5 × 1.5-cm polypoid distal esophageal mass. The squamocolumnar junction with strategies to make such accurate testing more widespread. The panel is committed to changing the guideline when and if data are provided to recommend those changes.

M. ELIZABETH H. HAMMOND, MD
Co-Chair, ASCO/CAP HER2 Guideline Panel
Intermountain Healthcare
LDS Hospital
Department of Pathology
Salt Lake City, UT 84143

ON BEHALF OF THE ASCO/CAP PANEL ON HER-2 TESTING IN BREAST CANCER

Malakoplakia Outside the Urinary Tract

To the Editor.—I read with great interest the comprehensive review of malakoplakia outside the urinary tract by Drs Yousef and Naghibi1 in the February 2007 issue of the Archives of Pathology & Laboratory Medicine and wish to complement their review by reporting a case of malakoplakia occurring in Barrett esophagus, a site and an associated condition that are yet to be reported.

A 93-year-old man presented with anemia and a 1-week history of weakness and melena. An upper gastrointestinal endoscopy revealed small gastric ulcers and a 2 × 1.5 × 1.5-cm polypoid distal esophageal mass. The squamocolumnar junction
was at 25 cm, and the gastroesophageal junction was at 35 cm. Esophageal biopsies were performed. No specific treatment was given. He died 20 months later. An endoscopy prior to death showed active bleeding from the esophageal mass and absence of gastric ulcers. There was no history of carcinoma.

Histologically, the biopsy specimen showed a Barrett esophagus with glandular mucosal tissue that contained scattered goblet cells (Figure, A). One tissue fragment contained sheets of histiocytes, accompanied by scattered lymphocytes and plasma cells, expanding the interglandular spaces (Figure, B). The histiocytes had finely granular cytoplasm. Scattered histiocytes contained Michaelis-Gutmann bodies that were peri-odic acid–Schiff and von Kossa stain positive (Figure, B through D). The larger bodies often had a targetlike or bull’s-eye appearance.

The gastrointestinal tract is, next to the urinary tract, the second most prevalent site for malakoplakia. Gastrintestinal malakoplakia usually involves the colorectum, and it has been associated with many conditions such as carcinoma, colonic polyps, ulcerative colitis, colonic diverticulosis, gastric ulcer, neurofibromatosis, alcoholic cirrhosis, colonic lymphoid hyperplasia, and tuberculosis.1,2 Upper gastrointestinal involvement is limited to a few cases of gastric or duodenal involvement.3–6 The present report appears to be the first report of esophageal malakoplakia. The significance of the association of malakoplakia and Barrett esophagus remains to be elucidated.


The author has no relevant financial interest in the products or companies described in this article.

Malakoplakia Outside the Urinary Tract

To the Editor.—Yousef and Naghibi,1 in their recent review of malakoplakia, have a table of published reports of malakoplakia outside the urinary tract. In that table corresponding to “testis,” they list an article from 2002 by Répássy et al,2 which is a case report of malakoplakia involving the prostate gland. The introduction of the article by Répássy et al has an unreferenced statement about instances of malakoplakia in testicles, lungs, and alimentary tract.

A search of my admittedly incomplete files reveals reports3–5 of malakoplakia (including some as granulomatous orchitis) in the testis, encompassing at least 20 examples by the early 1980s. I am sure that a search of my files reveals reports of malakoplakia involving the testicles in testicles, lungs, and alimentary tract.

To the Editor.

In Reply.—It is interesting to document the first case of malakoplakia of the esophagus. It is not surprising to find malakoplakia in the esophagus because the gastrointestinal tract is the second most common site of involvement after the urinary tract.1 An important differential diagnosis in this case would be that this nodule of malakoplakia occurred in an area of intestinal metaplasia of the gastriccardia. Malakoplakia has been documented to be related to conditions of chronic prolonged illness and immunosuppression. Regardless of the location, it is interesting to find this association with intestinal metaplasia, which can be viewed as a body response to chronic acid stress. Because many organisms have been implicated in the pathogenesis of malakoplakia, it will be interesting to further investigate the possible association of Helicobacter pylori and malakoplakia. A single previous report failed to find such a connection.3 In the gastrointestinal tract, malakoplakia has been reported in association with malignant and premalignant conditions. This report is the first showing an association with metaplasia.

We would like to thank the author of the second letter for the valuable observation. We fully agree that malakoplakia of the testis has been established in the literature for decades and that it is important it always be included in the differential diagnosis. In addition to presenting as a testicular mass, malakoplakia can also involve the epididymis4 and rarely occur as a paratesticular mass.4

KARL T. K. CHEN, MD
Department of Pathology
Saint Agnes Medical Center
Fresno, CA 93720

GEORGE M. YOUSEF, MD, PhD,
FRCP
Laboratory Medicine
St Michael’s Hospital
Toronto, Ontario, Canada
MSB 1W8

BIBI NAGHIBI, MD, FRCP
Department of Pathology
Eastern Health
St John’s, Newfoundland,
Canada A1C 5B8


The author has no relevant financial interest in the products or companies described in this article.

Letters to the Editor

Relevance of the Autopsy as a Medical Tool: A Large Database of Physician Attitudes

To the Editor.—I read with interest the article by Hooper and Geller1 in the February 2007 issue of the ARCHIVES. The authors did not examine what appears to be the major factor accounting for the 90% decrease in autopsies: a caref ul and complete autopsy is a time-consuming and expensive procedure involving multiple people, expensive supplies, and a significant capital expenditure. Pathologists are not eager to do them without compensation. Insurance companies and governmental health payors do not pay for autopsies claiming that they are not a patient service because the patient is dead and therefore there is no patient. Hospitals also are understandably reticent to pay for autopsies because they are under major financial constraint. In the last 20 years I have found that the only willing payors are coroner’s offices, trial lawyers, and families considering an adverse action procedure. Hence, the majority of cases done now fit into the category of forensic medicine.

The solution to the problem would seem to be obvious although the implementation is likely impossible. Therefore, any change in the current pattern is unlikely.

THOMAS A. STOLEE, MD
Marco Island, FL 34145


The authors have no relevant financial interest in the products or companies described in this article.

In Reply.—We thank Dr Thomas Stolee for his letter and observations regarding causes for declining autopsy rates. Although the hypothesis on diminishing payors is interesting and we agree with it in the main, the comments miss the thrust of our article. We set out to document the attitudes of physicians toward the autopsy as a medical tool and relate these attitudes to certain physician demographics. We did not undertake to explain or chronicle those factors external to the profession that may have contributed to autopsy decline. Thus, the letter aims well beyond the goals of our article, although it may well be within the scope of a future article on this topic. We are pleased to be able to participate in the continuing dialogue on this important subject.

JODY E. HOOPER, MD
STEPHEN A. GELLER, MD
Department of Pathology and Laboratory Medicine
Cedars-Sinai Medical Center
Los Angeles, CA 90048

The authors have no relevant financial interest in the products or companies described in this article.

Cutaneous Pulse Granulomas

To the Editor.—In the December 2006 issue of the ARCHIVES, Rhee and Wu1 reported 3 cases of pulse granuloma. One example was of a cutaneous pulse granuloma associated with abdominal fistula formation, which they claimed to be the first example of cutaneous pulse granuloma. In fact, Ferguson and Smillie2 reported what we believe to be the first documented example of a cutaneous pulse granuloma in 1986. That case concerned a 37-year-old dentured man who developed an orofacial sinus, which showed features of pulse granuloma histologically. Following that case, Martin et al3 reported an additional example of this condition in 1993, under the synonym of cutaneous giant cell hyalin angiopathy. As Rhee and Wu1 rightly point out, pulse granulomas most typically occur in the mouth with occasional examples reported in the lung and rectum.

We have recently observed 2 cases of cutaneous pulse granuloma.

Case 1 was a 35-year-old woman who presented to a dermatologist with a nonhealing lesion on the medial aspect of the left buttock. It had been present for more than 12 months and had failed to respond to several courses of systemic antibiotics. The patient believed the lesion may have developed following minor trauma. Clinically, the lesion was a small erosion with surrounding erythema. No sinus was identified, and there was no further significant medical history. The area was excised with a small skin ellipse. Histology showed reactive acanthosis with granulation tissue in the underlying dermis. Within this were scattered multinucleated histiocytes with aggregates of hyaline eosinophilic material, some of which surrounded vessels. Small fragments of birefringent foreign material were also present (Figure 1) with tiny foci of calcification and hemosiderin. The hyaline deposits were negative with crystal

Figure 1. Case 1 shows prominent hyaline material deposited in the dermis among granulation tissue in this example of a pulse granuloma (periodic acid–Schiff, original magnification ×100).

Figure 2. In case 2, the pulse granuloma shows irregular hyaline material in the dermis associated with some granular black pigment deposition and occasional multinucleated giant cells (hematoxylin-eosin, original magnification ×100).
violet and Congo red stains for amyloid, with the features in keeping with a pulse granuloma. Further questioning of the patient revealed that the lesion had probably been initiated by a wood splinter. There was complete resolution after the biopsy.

Case 2 was a man of 65 years who presented with a perianal lesion with clinical features suggestive of a small sinus or fistula. The lesion was excised with a small skin ellipse. Histology showed a foreign body type inflammatory reaction in the dermis with a little birefringent foreign material. Scattered foci of pale hyaline eosinophilic material were present, with some surrounding the walls of occasional vessels (Figure 2). Stains for amyloid were negative. A cleft in the tissue suggested formation of a small fistula, but no epithelial lining was evident histologically. There was no history of local trauma or inflammatory bowel disease, but the patient did report having had a possible piercing. There was evidence histologically. There was no history of local trauma or inflammatory bowel disease, but the patient did report having had a possible piercing.

In conclusion, pulse granulomas may exceptionally occur in the skin. This report brings the total number of cases in the literature to 5. It is notable that all reported cases of cutaneous pulse granulomas have occurred in skin close to openings of the gastrointestinal tract (Table). From the context of previous examples, and the features in these 2 new cases, it seems likely that the phenomenon is an unusual foreign body reaction to implanted material, often of vegetable nature. This should not be mistaken for amyloid deposits or some form of odontogenic derivative (calcifying odontogenic hyalin ring granuloma).4

TREVOR W. BEER, MBChB, MRCPath, FRCPA
Department of Pathology, Cutaneous Pathology
Nedlands, WA 6009, Australia

JUDY M. COLE, MBBS, FACD
Department of Dermatology
St John of God Dermatology
Subiaco, WA 6008, Australia


The authors have no relevant financial interest in the products or companies described in this article.

Emergency Transfusion of Incompatible Red Blood Cells

To the Editor.—Only minimal data are available to guide clinicians managing a patient with a life-threatening hemorrhage, a positive antibody screen, and serologic incompatibility with all available red blood cells (RBCs). Often, there is insufficient time or technical resources to perform a monocyte monolayer assay or other supplemental testing to predict whether the antibody (or antibodies) is likely to be clinically significant.1 Envisioning descriptions of catastrophic ABO-related hemolytic reactions, many clinicians interpret the laboratory’s report as an absolute contraindication and withhold transfusions.

Confronted with a case matching this scenario, we decided that transfusing serologically incompatible RBCs was a lesser risk than withholding transfusion. We would like to share our experience with the goal of encouraging others to report their cases and consider developing guidelines for transfusing incompatible RBCs.

A 62-year-old woman presented with a life-threatening gastrointestinal hemorrhage. Her hematocrit was 14%. Twelve days previously, her antibody screen was negative and she was transfused with 2 units of RBCs. Now, her antibody screen was posi-
The Role of Gadolinium in Triggering Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy

To the Editor.—We recently published a case report entitled “Nephrogenic Systemic Fibrosis Mimicking Inflammatory Breast Carcinoma” in the January 2007 edition of the ARCHIVES.1 This scleromyxedema-like systemic fibrosing disorder, the cutaneous manifestations of which led to the former appellation nephrogenic fibrosing dermopathy, was first recognized in 1997. As we stated in our article, Cowper and colleagues had suspected deposition of a recently introduced material, such as a contrast agent, medication, or allergen in peripheral tissues as the inciting agent. In this regard, a number of publications have subsequently appeared implicating the paramagnetic contrast agent gadolinium—more specifically, gadodiamide (Omniscan)—as a factor possibly contributing to the development of nephrogenic systemic fibrosis (NSF). We would like to share this new information with the readers.

Gadodiamide was approved in 1993 for magnetic resonance imaging

VIVIANA JOHNSON, MD
Department of Pathology and Laboratory Medicine
National Naval Medical Center
Bethesda, MD 20889

ALBERT LANGEBERG, MT
MOIN AHMAD, MD
S. GERALD SANDLER, MD
Department of Laboratory Medicine
Georgetown University Hospital
Washington, DC 20007


The authors have no relevant financial interest in the products or companies described in this article.

The views expressed in this article are of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the US Government.
but was not routinely used in patients with chronic renal insufficiency until 1997. Contrast-enhanced magnetic resonance angiography is often used to evaluate patients with renal failure for transplant eligibility, for visualization of vascular anatomy, or for posttransplant complications. Gadolinium-based contrast media are considered less nephrotoxic than their iodinated counterparts. Gadolinium-based contrast agents are formulated with excess chelate, because free Gd$^{3+}$ is highly toxic. Of the 5 gadolinium chelates available in the United States, gadodiamide has one of the higher acid dissociation rates and a lower thermodynamic stability. Therefore, this agent must be prepared with a relatively high concentration of chelate to minimize the amount of Gd$^{3+}$ formed in vivo. The half-life of gadodiamide in healthy patients is less than 2 hours, but it can exceed 120 hours in patients with renal insufficiency.

The first study temporally associating gadodiamide with NSF was reported by Gröbner in Austria. He identified 9 dialysis patients who received gadodiamide during a 2-year period, 5 of whom developed the characteristic skin findings of NSF 2 to 4 weeks following the procedure. Furthermore, those affected patients had a longer mean dialysis period and also were acidotic at the time of contrast injection. Gröbner suggested that the acidosis would facilitate the dissociation of the gadolinium-chelate complex, thereby promoting the accumulation of free Gd$^{3+}$ or chelate in tissues. In a subsequent Danish study, Markmann et al showed that 13 of 370 patients exposed to gadodiamide for magnetic resonance arteriography of iliac and lower limb vessels developed NSF during a 10-month period. The delay from exposure to first sign of the disease was 2 to 75 days (median, 25 days). The odds ratio for acquiring the disease when exposed to gadodiamide was 32.5. Markmann et al did not find an association with acidosis, but laboratory data were only available for 3 affected patients. More recently, Broome et al investigated 559 magnetic resonance examinations (301 were contrast-enhanced with gadodiamide) performed on 168 dialysis patients from 2000 through 2006. Twelve patients (8 dialysis-dependent and 4 with the acute hepatorenal syndrome) were diagnosed with NSF. All affected patients developed characteristic skin changes 2 to 11 weeks after gadodiamide administration. The calculated odds ratio for developing NSF following gadodiamide exposure was 22.3.

Two additional studies have detected the deposition of gadolinium in skin biopsies of patients with NSF. High et al used a field emission scanning electron microscope equipped with energy dispersive spectroscopy to detect gadolinium in 4 of 13 tissue specimens from 7 affected patients. The gadolinium was localized to dermal macrophages in the interstitium. Based on the known exposure history of patients with detectable gadolinium, a tissue residence time of 4 to 11 months was observed. In the second study, Boyd et al also used a scanning electron microscope equipped with energy dispersive spectroscopy to detect gadolinium in tissue samples from 4 patients with NSF. The gadolinium was confined to areas of concomitant calcium, phosphate, and sodium deposition in vessel walls. In 1 case, gadolinium was also found to be in a peri-eccrine distribution.

These studies among others have prompted the US Food and Drug Administration to issue a public health advisory, warning health care providers about the risks of administering gadolinium-based contrast agents to patients with moderate-to-severe renal failure. Future studies are warranted to understand the possible role of gadolinium-based contrast agents—as well as the potential contributory roles of surgery and thrombotic episodes—in triggering NSF. It is imperative that physicians, particularly radiologists and nephrologists, be alerted to these new developments.

Garron Joseph Solomon, MD
Paul Peter Rosen, MD
Pathology and Laboratory Medicine
New York Presbyterian Hospital—Weill Medical College of Cornell University
New York, NY 10021
Elizabeth Wu, MD
Department of Pathology
New York Methodist Hospital
Brooklyn, NY 11215


The authors have no relevant financial interest in the products or companies described in this article.