

What the heck is this new periductal hypoechoic sign?

What the heck is that thing? . . . I dunno! This is starting to sound like a Saturday Night Live skit that Steve Martin and Bill Murray used to do.¹ In this month's issue of *GIE*, Sawhney et al² describe a previously undefined sign that they demonstrate with EUS in patients suspected of having pancreatic cancer. They report that this new periductal hypoechoic sign (PHS) is associated with the finding of malignancy in patients who have a dilated pancreatic duct. Why has this finding only come to our attention now after more than 20 years of performing EUS on thousands of patients? What exactly are we seeing here? Moreover, is this sign really helpful in the clinical management of these patients? As is often the case with discoveries, science, and medicine, the more we see, the more questions we have. Or, in the lyrics of Don Henley, cofounder of the Eagles, "The more I know the less I understand."³

It seems odd that a sign such as this is noticed now after so many of us have been doing so many EUS examinations virtually all over the world for so long. How could we have missed something like this? One reason might be that we are often so busy and under so much pressure to be productive that we cannot or do not want to take the time to step back and simply observe what is happening around us with a curious mind. Thankfully some still do, so here we are assessing a brand new finding after all these years. Kudos should go to the authors for taking the first step and exploring a simple observation that they have made. The importance of simple observation in medicine cannot be overstated. Our microbiology professors in medical school would have us remember that Edward Jenner, an English country doctor, made the observation that his patients who worked with cattle and had come into contact with cowpox never came down with smallpox when an epidemic ravaged the countryside in 1788. That observation was an important step in the development of the vaccination against smallpox and subsequent vaccines, including those for the flu with which humanity will battle the H1N1 virus.

So now that this report² describes this new finding, what does this all mean? They defined the PHS as the presence of multiple, patchy, 1- to 2-mm hypoechoic

areas located in the pancreas parenchyma around the dilated main pancreatic duct. This finding was most prominent around the pancreatic duct just above the level of obstruction and became less prominent around the distal duct. Unfortunately, the authors' attempts to correlate these EUS findings with the findings of a pathologist have been unrevealing. One confounding factor was the inability to find adequate cross sections of the main pancreatic duct above the level of the tumor in the cases that they examined.

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The first question that comes to mind is what are these things? Some of the ideas proposed by the authors include small areas of pancreatitis caused by obstruction of small pancreatic duct side branches and localized spread of tumor cells. The suggestion that these are tumor cells in all these patients would seem to contradict the results because more than 10% of the patients with benign outcomes had the PHS. The fact is that without correlating the PHS with histological findings, we simply cannot say for sure what these images are indicating.

It turns out that obtaining correlations between EUS images and histologic findings can be quite complex, as was pointed out by one of the early practitioners of EUS, Dr Michael Kimmey.⁴ Some possibilities that could confound histologic correlations with the PHS include (1) a transient process that exists for a short period of time in vivo, (2) a process that exists in vivo that is not present after the pancreas specimen is removed at surgery, (3) a finding that is so subtle or small that it is difficult to locate by the pathologist, (4) more than 1 process, all of which produce similar images on EUS.

It is quite likely that to solve this mystery, extraordinary effort will be needed. To verify that this is not a transient process, verification of a persistent PHS could be demonstrated on sequential EUS examinations in the same patient. A set of these case studies would be

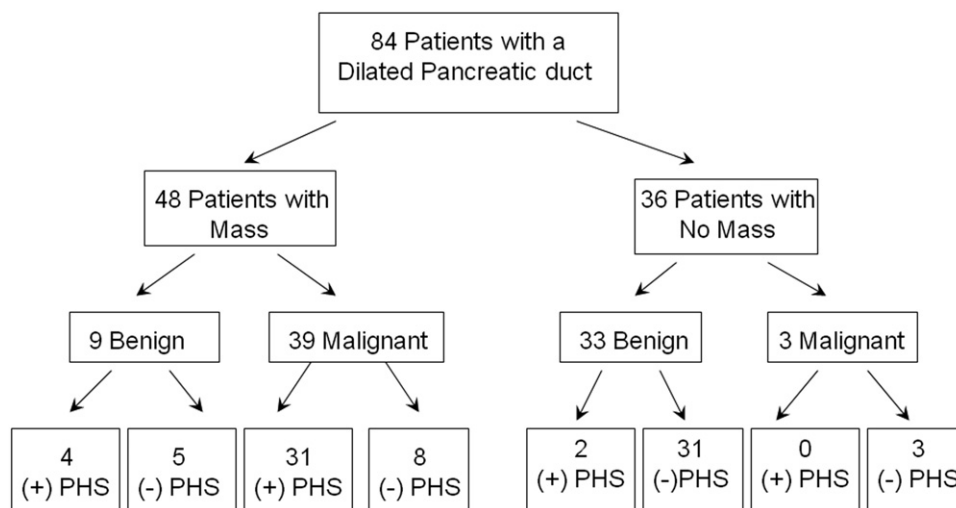


Figure 1. Summary of findings in patients with and without a mass.

interesting because it would provide useful information about whether the PHS was transient.

Another possible strategy would be to perform EUS to locate the PHS in a patient at the time that a Whipple procedure is performed. (Do not forget to have the surgeon clamp the distal small bowel for this one.) Obtaining exact measurements between a mass and the PHS upstream in the pancreatic duct would be very helpful to the pathologist. Even more helpful would be to inject ink next to the PHS with a needle under EUS guidance in the operating room just before the resection. Once again, a set of case studies of this type would be interesting because it would probably provide useful clues no matter what the findings were.

Perhaps most important would be the recruitment and participation of an interested surgeon and pathologist to help solve this problem. A strong incentive here would be that such a study would contribute to our understanding of EUS and the pathophysiology of pancreatic cancer; therefore, it should be considered for publication in some form even if it were a quick letter to the editor.

Even if the pathophysiology of a sign is not well understood, it can still be clinically useful. One of the best examples of that in this field is the Sister Mary Joseph sign.⁵ Sister Mary Joseph (1856-1939) was a surgical assistant to Dr William Mayo at St. Mary's Hospital in Rochester, Minnesota. She was able to predict malignant findings at laparotomy if she felt an umbilical mass while preparing the abdomen for surgery. Dr Mayo first reported the finding as "pants-button umbilicus" (without credit to Sister Mary Joseph) in a lecture to the Cincinnati Academy of Medicine in 1928.⁶ The term *Sister Mary Joseph's nodule* was proposed by Sir Hamilton Bailey in 1949 to accredit Dr Mayo's assistant.^{7,8} Sister Mary Joseph may not have known what

this umbilical mass was, and the pathophysiology explaining how tumor cells migrated to the umbilical area is debatable. Nonetheless, the sign is well-known for its ability to predict a poor prognosis.

So even though we do not exactly know what it is, does this PHS provide us with valuable information? The authors report that the PHS had a sensitivity of 73.8%, a specificity of 85.7%, and an accuracy 79.8% for a diagnosis of pancreatic malignancy. After adjusting for age, patients with PHS had 17 times greater odds for malignancy (odds ratio 16.66; 95% CI, 5.01-55.44). Wow! That sounds impressive. But let us look at these data from the perspective of a clinician who is evaluating an individual patient. The authors state that the presence of a mass in the pancreas correlated strongly with other dependent variables and therefore could not be entered into the regression model. For the purposes of this study, that may be true. However, when we see a patient with a dilated pancreatic duct, most of the time, the same imaging that reveals the dilated duct also reveals, or does not reveal, a pancreatic mass. In fact, each patient in this study was classified as having or not having a pancreas mass.

With this in mind, if we take the data from this report along with data that were graciously provided by the authors through personal communication, we can construct the following: Eighty-four patients were included in the study. Of these, 48 had pancreatic masses and 36 did not. Of the 48 patients with a pancreatic mass, 9 were benign and 39 were malignant. Of the 9 benign masses, 4 had the PHS and 5 did not. Of the 39 patients with malignant masses, 31 had the PHS and 8 did not. Of the 36 patients without a pancreatic mass, 33 had benign findings and 3 had pancreatic cancer. The PHS was not found in the 3 patients with cancer, and 2 of the 33 patients with benign findings had the sign. This infor-

TABLE 1. Findings in patients with a mass

	Cancer		Totals
	Absent	Present	
PHS positive	4	31	35
PHS negative	5	8	13
Totals	9	39	48
	Estimated value	95% CI	
Sensitivity	0.79	0.63-0.90	
Specificity	0.55	0.22-0.84	
For a positive PHS result, the probability that it is			
True positive	0.88	0.72-0.96	
False positive	0.11	0.03-0.27	
For a negative PHS result, the probability that it is			
True negative	0.38	0.15-0.67	
False negative	0.61	0.32-0.84	

CI, Confidence interval; PHS, periductal hypoechoic sign.

TABLE 2. Findings in patients without a mass

	Cancer		Totals
	Absent	Present	
PHS positive	2	0	2
PHS negative	31	3	34
Totals	33	3	36
	Estimated value	95% CI	
Sensitivity	0	0-0.69	
Specificity	0.93	0.78-0.98	
For a positive PHS result, the probability that it is			
True positive	0	0-0.80	
False positive	1	0.19-1.0	
For a negative PHS result, the probability that it is			
True negative	0.91	0.75-0.97	
False negative	0.08	0.02-0.24	

CI, Confidence interval; PHS, periductal hypoechoic sign.

TABLE 3. A comparison of the predictive values of a mass for cancer and the predictive values of a PHS for cancer in this study

Association of a mass with cancer in this study			
	Cancer		Totals
	Absent	Present	
Patients with a mass	9	39	48
Patients without a mass	33	3	36
Totals	42	42	84
	Estimated value	95% CI	
Sensitivity	0.92	0.79-0.98	
Specificity	0.78	0.62-0.89	
For patients with a mass, the probability that it is			
True positive	0.81	0.66-0.90	
False positive	0.18	0.09-0.33	
For patients without a mass, the probability that it is			
True negative	0.91	0.76-0.97	
False negative	0.08	0.02-0.23	

	Cancer		Totals
	Absent	Present	
PHS positive	6	31	37
PHS negative	36	11	47
Totals	42	42	84
	Estimated value	95% CI	
Sensitivity	0.73	0.57-0.85	
Specificity	0.85	0.70-0.94	
For patients with a PHS result, the probability that it is			
True positive	0.83	0.67-0.93	
False positive	0.16	0.06-0.32	
For patients without a PHS result, the probability that it is			
True negative	0.76	0.61-0.87	
False negative	0.23	0.12-0.38	

CI, Confidence interval; PHS, periductal hypoechoic sign.

mation is summarized in Figure 1. Using this information, we can calculate the sensitivity, specificity, predictive values, and their respective confidence intervals for the PHS in the group of patients with a mass and in the

group without a mass. The 2 × 2 tables and calculations for each group appear in Tables 1 and 2.

Although conclusive statements cannot be made because of the small numbers in these subsets, it is possible that for those patients with a mass, a negative PHS

most often will be a false negative. For those patients without a mass, the subsets have such small numbers that the significance of a positive PHS also cannot be determined. The 95% confidence intervals for positive and negative predictive values in this group are very wide.

Moreover, the 95% confidence intervals for the positive predictive value of a mass for cancer overlaps widely with the 95% confidence values for the positive predictive value of the PHS for cancer reported in this study (Table 3). So it is possible that a positive PHS is not likely to be significantly different from the presence of a mass when predicting cancer.

It should be emphasized that these data include small numbers from a retrospective study that focused on the PHS. Therefore, conclusive statements about the clinical usefulness of the PHS would be premature. Prospective studies should be done, especially in larger subsets of these patients.

The authors should be commended for revealing this new finding and starting it on the long road to becoming a sign (sorry for the pun). Now that it has been reported, more clinicians/investigators will be aware of its existence. As awareness is increased, perhaps additional experiences and studies regarding the significance and the pathophysiology of the PHS will be reported. With this additional information, we will be able to determine whether the PHS is a truly useful sign or another of the many findings in medicine that result from artifacts that seem to make little sense and/or have little clinical value. It is important that we separate the truly meaningful signs from the less meaningful ones so that we do not clutter our literature and clinical reports with so many signs of questionable value that we confuse ourselves as well as our patients. A predicament similar to that which the Five Man Electrical Band sang about in the chorus of their song about signs: "Signs, signs, everywhere there's signs. Blockin' up the scenery,

breakin' my mind. Do this, don't do that, can't you read the sign?"⁹

DISCLOSURE

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John Affronti, MS, MD

*Division of Gastroenterology, Hepatology, and Nutrition
Department of Medicine
Stritch School of Medicine
Loyola University of Chicago
Maywood, Illinois, USA*

Abbreviation: PHS, periductal hypoechoic sign.

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