Well-differentiated Neuroendocrine Carcinoma
A Designation Comes of Age

In this issue (see page 1053), Lequaglie and co-workers describe a retrospective analysis of their ten-year experience with resected, well-differentiated neuroendocrine carcinoma (WDNC). Their work confirms and extends the observations of others that WDNC is a clinicopathologic entity distinct from other neuroendocrine tumors of the lung, including carcinoid tumor and small cell lung carcinoma (SCLC).1,2 Utilizing morphologic criteria defined by Gould et al,3 the authors identify 19 cases of resected WDNC. Significantly, while six of the first 12 cases were diagnosed as atypical carcinoids, the remaining six cases had originally been diagnosed as SCLC, thereby reinforcing the observation that some WDNCs are mistaken for SCLC. Refinements in the morphologic diagnosis of WDNC by Warren and co-workers4 clearly demonstrate that, while the WDNC category encompasses tumors originally diagnosed as atypical carcinoids, it also includes tumors that may be incorrectly diagnosed as SCLC, particularly when diagnostic material is limited to small bronchoscopic biopsy specimens or cytologic preparations. In our experience,5 these cases represent a large majority of long-term survivors with a diagnosis of SCLC. Similar morphologic observations have been made in cytologic studies of bronchial specimens, and criteria have been established for the cytodiagnosis of WDNC.6

In their analysis of the clinical data, Lequaglie and co-workers suggest that surgery may be the treatment of choice for patients with localized WDNC. Prospective studies based on careful histologic subtyping and clinical staging should define the role of primary surgical therapy and adjuvant therapies in the treatment of patients with WDNC. Additionally, immunohistochemical and flow cytometric analyses of these tumors may provide adjunctive prognostic data useful in the management of WDNC.5,6 Immunohistochemical studies of SCLC with monoclonal antibody SCCL 175, an antibody directed against SCLC, have shown that the expression of the antigen defined by this antibody can distinguish WDNC and SCLC and that its expression is associated with shorter patient survival times.5 The use of flow cytometric DNA analysis is still unclear, although it also may provide supportive prognostic information in classifying neuroendocrine carcinomas of the lung.

The strength of any tumor classification system depends on its ability to be reproducibly applied by pathologists and its utility to clinicians for the treatment of patients. Mounting evidence indicates that recognition of WDNC as a distinct type of pulmonary neuroendocrine neoplasm fulfills these criteria. The prospective recognition of WDNC will allow the development of new therapeutic modalities. Meanwhile, it is also clear that new tools must be found to objectively define the different neuroendocrine carcinomas of lung.

Vincent A. Memoli, M.D.
Hanover, New Hampshire

Dartmouth-Hitchcock Medical Center.

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Management of Parapneumonic Effusions

Approximately 40 percent of patients with acute bacterial pneumonia will have an associated pleural effusion.1 Most of these parapneumonic effusions will resolve with only the administration of antibiotics.1,2 I have used the term complicated parapneumonic effusion for a parapneumonic effusion that requires tube thoracostomy for resolution or which has a culture positive for bacteria.1 In the clinical situation, one would like to identify as early as possible those individuals who will need chest tubes, since a free-flowing complicated parapneumonic effusion can progress to a multiloculated effusion in a matter of hours.3 Once the complicated parapneumonic effusion becomes loculated, its management is much more difficult.1,5

Whether or not an individual with a parapneumonic effusion requires tube thoracostomy depends on several different factors. The bacteria responsible for the underlying pneumonia are important; parapneumonic effusions due to Staph aureus or anaerobic bacteria
are more likely to require chest tubes than are those due to *Strep pneumoniae*. The immunologic competence of the patient is important; young trauma victims usually do not require chest tubes even when the cultures of the pleural fluid are positive for bacteria. Patients with more bacteria in the pleural space are more likely to need chest tubes. Patients with loculated parapneumonic effusions are more likely to require chest tubes, although not all loculated parapneumonic effusions require tube thoracostomy. The smaller the pleural effusion, the less likely tube thoracostomy will be necessary.

In general, one relies on the characteristics of the pleural fluid to identify which patients will need a chest tube. However, in view of the multiple factors influencing the prognosis of a parapneumonic effusion, it is not surprising that any one laboratory test is not 100 percent specific and sensitive in identifying which patients will require chest tubes. Unquestionably, tube thoracostomy should be performed if gross pus is obtained with the diagnostic thoracentesis. Although this test is specific, it is not sensitive. In the retrospective series reported by Poe et al in this issue of *Chest* (see page 963) only 9 of the 27 patients (33 percent) who received chest tubes had pus on thoracentesis. The presence of a positive pleural fluid Gram stain is a more sensitive test, but is less specific since some patients with a positive Gram stain will recover without chest tubes, as shown in the article by Poe and colleagues.

We have previously recommended that if the pleural fluid glucose is below 40 mg/dl, or if the pleural fluid pH is below 7.00, tube thoracostomy should be performed immediately. Moreover, we have stated that if the pleural fluid pH is between 7.00 and 7.20, or if the pleural fluid lactic acid dehydrogenase (LDH) is above 1,000 IU/L, the patient may require a chest tube. In such situations, serial thoracentesis may be worthwhile; if with serial thoracentesis the pH and glucose increase while the LDH decreases, chest tubes will probably not be necessary.

Poe and co-workers conclude from their retrospective analysis of 91 patients with parapneumonic effusions that measurement of the pleural fluid glucose, pH and LDH has limited usefulness in predicting the need for eventual chest tube drainage and/or decortication. I would argue that their data do not support this conclusion. If patients with frank empyema are excluded from their analysis, 10 of the 18 patients (56 percent) who had a pleural fluid pH value below 7.00 and/or a pleural fluid glucose below 40 mg/dl required chest tubes. In contrast, only 8 of 52 patients (15 percent) who did not meet these criteria received tube thoracostomy. In other words, patients who met one or both of the criteria were more than three times as likely to need tube thoracostomy ($\chi^2 = 9.29$, $p<0.005$).

In addition, from their Figure 2, it appears that the glucose and pH levels are higher and LDH levels lower in the individuals who were never subjected to tube thoracostomy, although there is substantial overlap. Lastly, the reasons for the tube thoracostomy or decortication in the reported study are not completely delineated. It is quite possible that some of the patients may have been treated because of pleural loculation or pleural thickening rather than pleural sepsis and such patients would not necessarily be expected to have a low pleural fluid glucose or pH.

In summary, when a patient with a parapneumonic effusion is identified, it is recommended that thoracentesis be performed immediately. If frank pus is obtained or if the Gram stain of the pleural fluid is positive, tube thoracostomy should be performed without delay. It is also recommended that almost all patients with a pleural fluid glucose value below 40 mg/dl or a pleural fluid pH below 7.00 undergo tube thoracostomy. Although some of the patients will recover without placement of chest tubes, the majority will not. The extra morbidity associated with delayed tube thoracostomy justifies the placement of a few extra chest tubes. If the pleural fluid cultures are positive, the pleural fluid pH between 7.00 and 7.20, or the pleural fluid LDH is above 1,000 IU/L, consideration should be given to tube thoracostomy particularly if the pleural fluid is loculated or the effusion is large. If the patient has a negative pleural fluid culture, pleural fluid glucose above 40 mg/dl, and pH above 7.20, tube thoracostomy is not indicated even if the effusion is loculated. However, if the patient does not respond clinically, or if the pleural effusion increases in size, the patient should be reevaluated with another thoracentesis.

Richard W. Light, M.D.,* F.C.C.P.*
Long Beach, California
Associate Chief of Staff for Research and Development, VA Medical Center; Professor of Medicine, University of California Irvine.

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