

False-Positive Sputum Cytology in a Case of Pulmonary Infarction

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Sputum cytology is an important diagnostic tool in pulmonary medicine, but it can yield a false-positive diagnosis of malignancy. We describe such a case, which involved a 70-year-old man who presented with chest pain, hemoptysis, and bilateral pulmonary infiltrates. In the initial evaluation of hemoptysis, multiple sputum samples demonstrated cytological abnormalities consistent with adenocarcinoma, but bronchoscopy found no evidence of malignancy. He was ultimately found to have pulmonary thromboembolic disease with infarction. Follow-up radiographs showed resolution of the pulmonary infarcts, and the absence of malignancy was proven during postmortem examination. Pulmonary infarction is one of many diseases that can produce sputum cytological findings falsely indicative of malignancy. Key words: sputum, cytology, malignancy, adenocarcinoma, pulmonary infarction. [Respir Care 2004;49(2):186–188. © 2004 Daedalus Enterprises]

Introduction

One of the most challenging problems in pulmonary clinical cytopathology is distinguishing atypical pneumocytes from adenocarcinoma.¹ Atypical pneumocytes can arise from various injurious processes occurring in the lung, among which is pulmonary infarction. Though this finding is well-described in cytopathology textbooks, it has not appeared previously in the English literature in journals of respiratory medicine, and the English literature dates back to the 1980s and earlier. We report a patient who had atypical pneumocytes suspicious for adenocarcinoma seen on examination of sputum and bronchial washings, but which proved to be due to pulmonary infarction.

Case Summary

A 70-year-old white male nonsmoker with a history of congestive heart failure presented with sudden onset of dyspnea, right pleuritic chest pain, and hemoptysis. On examination the patient was in mild respiratory distress,

with a respiratory rate of 22 breaths per minute and his oxygen saturation (measured via pulse oximetry, while breathing room air) was 93%. He was in atrial fibrillation; heart rate was 84 beats/min; blood pressure was 150/60 mm Hg. Pertinent physical findings included jugular venous distension, distant heart sounds without murmur, dullness to percussion at both lung bases, with bilateral, coarse, mid-zone crackles, and bilateral lower-extremity edema. Laboratory evaluation, including complete blood count and chemistries, was normal. A chest radiograph and computed tomogram (CT) revealed bilateral pleural opacities, with cardiomegaly and bilateral pleural effusions. A deep venous ultrasound revealed a clot within the right popliteal vein.

Along with the deep vein thrombosis the patient was presumed to have bilateral pulmonary emboli with infarction, on the basis of the pleural-based opacities seen on CT. He was also diagnosed with worsened congestive heart failure, and treatment was started with intravenous heparin. We also continued his furosemide, enalapril, and digoxin. Because of concern about underlying malignancy in the setting of hemoptysis, 2 sputum samples were sent for cytology. The specimens revealed few atypical cells, lying singly or in cohesive, gland-like clusters. The cells were large (15–20 microns in diameter), as compared with normal and reactive bronchial cells. The cells were round to elongated, some having copious basophilic cytoplasm, others displaying hypervacuolation. Nuclei were round but showed some pleomorphism in size and shape. Nuclear margins were well defined and generally smooth. Nuclear

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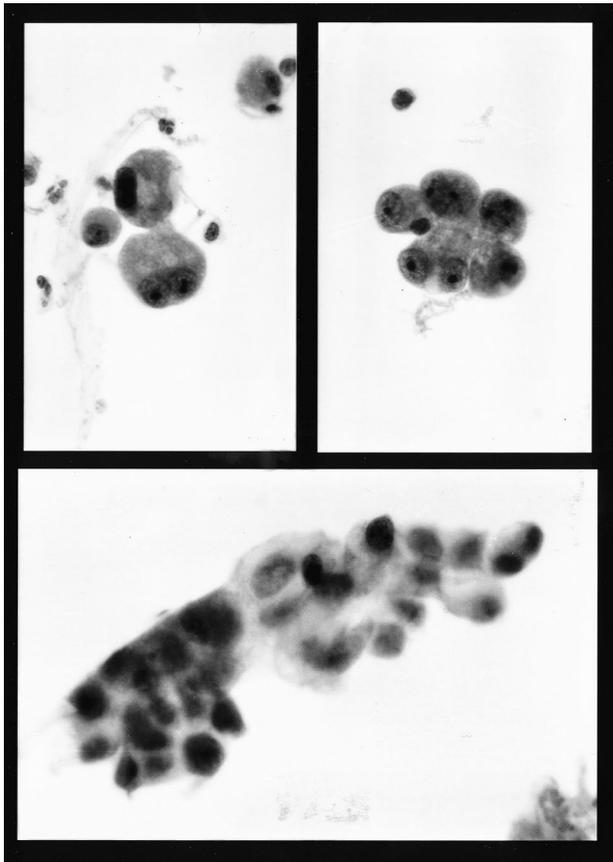


Fig. 1. Sputum cytology (Papanicolaou stain, magnification 400 \times). Top Left: A group of 3 pneumocytes is in the center of the field, surrounded by rare polymorphonuclear and histiocytic inflammatory cells. One of the 3 pneumocytes is of normal size, permitting appreciation of the marked cellular enlargement of the other 2 cells, one of which demonstrates binucleation and macronucleoli. Top Right: A cohesive cluster of round-to-oval pneumocytes. The large size of these pneumocytes can be assessed in comparison with 2 lymphocytes in the field, one overlying the cell group. Two of the cells show very high nuclear-to-cytoplasmic ratios; the remainder demonstrate eccentrically placed nuclei and more abundant granular cytoplasm. Bottom: A cluster of atypical pneumocytes. Areas of the image are out of the plane of focus, due to 3-dimensionality. In the center of the group are cells demonstrating more vacuolated cytoplasm.

chromatin was finely granular, with a tendency to chromatin clumping in occasional nuclei. Prominent macronucleoli were easily observed and these cells were reported as suspicious for adenocarcinoma (Fig. 1), although the cytopathologist commented that "in light of the clinical history, the cells could also be in the spectrum of severe reactive changes associated with (pulmonary) infarction." This finding and interpretation was agreed upon by at least 2 cytopathologists. Bronchoscopy was subsequently performed one week after the collection of the initial sputum sample, at a time when the patient appeared to be improving clinically, and revealed no evidence of any endobron-

chial lesions. Bronchial washings were positive for the same cellular findings as the sputum specimens, although there were fewer abnormal cells than the initial sputum studies ("very rare" compared to "few"), and cellular degeneration was more evident. A transbronchial biopsy specimen of one of the regions of parenchymal abnormality seen on CT was negative for malignancy.

The patient was treated for thromboembolic disease and congestive heart failure, and he slowly improved. A follow-up chest CT showed substantial resolution of the parenchymal opacities, consistent with pulmonary infarction. He was discharged in good condition. His chest radiograph gradually cleared and he had no further hemoptysis. However, his congestive heart failure progressed, and he died of refractory ventricular tachycardia 3 years later. Post-mortem examination of the lungs showed signs of vascular congestion, but there was no evidence of malignancy in the lungs or elsewhere.

Discussion

This case illustrates one of the most common diagnostic dilemmas in sputum cytology, namely, distinguishing reactive changes from true malignancy.¹ Though the specificity of sputum cytology for malignancy is above 90%,² many disease processes, all of which involve pulmonary inflammation or injury, may lead to false-positive cytological changes. These diseases include pulmonary infarction, viral infections, organizing pneumonia, pulmonary fibrosis, granulomatous diseases, congestive heart failure, diffuse alveolar damage, and toxicity due to oxygen, drugs, or irradiation.³

Atypical type II pneumocytes are thought to be the primary cell involved in causing false-positive cytological findings.^{1,3} The type II cell proliferates in response to inflammation or injury, leading to changes that may easily be mistaken for adenocarcinoma. In a dog model of pulmonary infarction such atypia occurred maximally 4–7 days after infarction,⁴ and the changes consisted of isolated clumps and individual cells with enlarged nuclei, increased nuclear-to-cytoplasmic ratio, large multiple nucleoli, and marked pleomorphism. The cells were thought to arise from the terminal bronchioles and alveoli. Interestingly, this is also the area from which bronchoalveolar cell carcinoma originates, a diagnosis often mistakenly made in the presence of pulmonary infarction.

Two case series have described the cytological features of lung cells from patients with pulmonary infarcts and false-positive cytological diagnoses of lung carcinoma. In 1977 Scoggins et al⁵ described 15 patients who were found to have false-positive diagnoses of malignancy, of whom three had pulmonary infarction. The authors retrospectively identified certain characteristics that may have favored a benign diagnosis: small numbers of atypical cells,

variable morphology of cells, poor nuclear detail, lack of depth-of-focus, common cell border, and tight clustering of cells.⁵ Other clues to abnormal cells being due to reactive hyperplasia or repair rather than malignancy include distinct cell borders, smooth nuclear membranes with uniform nuclei, and vesicular or fine chromatin.^{3,5,6}

In 1983 Bewtra et al⁶ described the cytological features of lung cells from 9 patients with pulmonary infarction. Maximal cellular changes occurred during the second and third weeks after diagnosis and were similar to those described from a dog model⁴ and the report by Scoggins et al.⁵ In addition, Bewtra et al pointed out the transient nature of the cytological changes, and both Bewtra et al and Scoggins et al suggested that in cases of suspected pulmonary embolism, cytology should be performed again at a later date.

Our case illustrates many of these features. Favoring malignancy there were strikingly suspicious morphological changes, especially the very granular chromatin pattern and the fact that so many of the cells lay singly. Against malignancy were many of the features described above associated with reactive hyperplasia and repair, including the observations that cell morphology was variable and that specimens obtained at a later date showed fewer ab-

normal cells. Of course, the clinical setting also suggested the alternative diagnosis of pulmonary infarction.

In summary, this case illustrates the importance of recognizing a false-positive cytological diagnosis of malignancy in the setting of pulmonary infarction.

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