Pulmonary Radiofrequency Ablation Complicated by Acute Respiratory Distress Syndrome

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ABSTRACT

The authors present a case of a patient with rectal adenocarcinoma and lung metastasis undergoing elective radiofrequency (RF) ablation of a large, refractory pulmonary metastasis. The mass was located in the left upper lobe, invading the left hilum. The patient experienced shortness of breath following the procedure and shortly after extubation. This shortness of breath progressed over 4 days, when the patient developed acute respiratory distress syndrome (ARDS). The patient suffered from complications related to respiratory support and expired 9 days after RF ablation. Possible mechanisms of ARDS development following pulmonary ablation are discussed.

KEYWORDS: Radiofrequency ablation, lung cancer, complications

CASE REPORT

The patient initially presented with T3N0 rectal carcinoma. After downstaging chemoradiation, the patient underwent proctectomy with coloanal anastomosis. Less than 2 years later, the patient was discovered to have multiple pulmonary metastases on follow-up chest computed tomography (CT). The patient was treated with irinotecan and 5-fluorouracil for metastatic disease, demonstrating good initial response. After 18 months, the patient was found to have progressive pulmonary disease on CT and was changed to a FOLFOX (leucovorin, fluorouracil, and oxaliplatin) and bevacizumab (Avastin) protocol. The patient did not respond to the new therapy and was referred to the Interventional Radiology service for possible debulking of a progressive left upper lobe metastasis that had begun to invade the left hilar vessels (Fig. 1). Her ongoing chemotherapy was held for 3 weeks prior to the ablation.

Pulmonary RF ablation was performed under general anesthesia. A 16-gauge (16G) cool-tip RFA needle was used, repositioned 3 times to ablate the superior, inferior, and lateral aspect of the $4.1 \times 2.7 \times 2.4$ cm mass. At each position, ablation was performed for 16 minutes per protocol, based on time and impedance. Immediate follow-up CT demonstrated a small pneumothorax, which did not require chest tube placement. The patient was short of breath upon extubation. The patient required supplementary oxygen and was admitted for observation.

Post-RF ablation day 1, the patient felt subjectively better; however, the patient continued to require supplemental oxygen and was noted to desaturate ($\text{SaO}_2 \sim 80\%$) while talking. Chest radiographs demonstrated diffuse alveolar infiltrates consistent with pulmonary edema. That evening, the patient became progressively tachycardic and tachypneic, and was transferred to the

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Figure 1 Axial computed tomography image revealing a 4-cm left hilar mass.

intensive care unit. A CT scan was obtained; revealing a nonspecific, diffuse ground glass appearance (Fig. 2).

Post-RF ablation day 3, the patient was intubated for progressive respiratory failure. Post-RF ablation day 4, her ratio of arterial oxygenation to inhaled oxygen ($\text{PaO}_2/\text{FiO}_2$) was 120 and her pulmonary wedge pressure was less than 15. This severe inability to oxygenate despite high PaO_2 ($\text{PaO}_2 / \text{FiO}_2 < 200$), without evidence of heart failure, confirmed the diagnosis of adult respiratory distress syndrome (ARDS). Bronchial-alveolar lavage demonstrated multiple red blood cells (RBCs), consistent with alveolar hemorrhage. Post-RF ablation day 5, the patient experienced a devastating anoxic episode during endotracheal tube exchange. This was complicated by bilateral pneumothoraces with a large right-sided air leak. Post-RF ablation day 8, the patient showed no response to painful stimuli despite no sedation for the prior 24 hours. The patient expired 9 days after her ablation.

Figure 2 Axial computed tomography image obtained 2 days after pulmonary radiofrequency ablation. There are scattered, bilateral ground glass opacities.

At autopsy, the lungs demonstrated diffuse masses consistent with metastatic colon cancer. Microscopic evaluation revealed diffuse organizing fibrosis, hyaline membranes, type II pneumocyte proliferation, and squamous metaplasia. These findings were consistent with diffuse alveolar damage, organizing phase. These are the typical pathological findings in ARDS. No microscopic evidence of infection or aspiration was found.

DISCUSSION

Very few deaths due to complications from RF ablations have been reported: 2 from direct damage to the pericardium^{1,2} and 1 from shock not otherwise described during hepatic lesion ablation.³ The incidence of ARDS as a complication of pulmonary RFA is likely quite low, with no publications in the medical literature dedicated to this topic.

This patient presented herein presented for RF ablation of a refractory tumor and developed ARDS over 3–4 days. She expired less than 2 weeks after the procedure, never leaving the hospital. Determining the causal relationships between the elements of the case, the eventual diagnosis, and the outcome is difficult. The proximal causes of her death were complications related to respiratory support. Her diagnosis of ARDS was confirmed at autopsy.

The diagnosis of ARDS was defined by the European–American Consensus Conference on ARDS as impaired oxygenation in the setting of bilateral radiographic pulmonary infiltrates without evidence to of cardiac failure. The diagnosis is more specifically defined as a ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) less than 200 and a pulmonary-artery occlusion (wedge) pressure of less than 18.^{4,5} Unfortunately, determining which patients with pulmonary infiltrates and impaired oxygenation will progress to ARDS remains a clinical challenge. The diagnosis and preparation for appropriate supportive intensive care should be considered in all patients with new bilateral pulmonary infiltrates and increased oxygen dependence. Heightened consideration is appropriate in patients with relatively common predisposing conditions, such as sepsis, pneumonia, aspiration pneumonia, and hemorrhagic shock.⁶

Treatment of ARDS remains limited to supportive measures and appropriate treatment of any predisposing conditions. Many different therapies, including inhaled nitrous oxide, exogenous surfactant, glucocorticoids, new highly specific antiinflammatory agents, and empiric antibiotics have been proposed. Extensive research has failed to show sustained benefits for patients with ARDS, although multiple trials are ongoing.⁷

The mainstay of supportive therapy is mechanical ventilation. The greatest therapy-derived survival benefit

in ARDS came from the development of specific lung-sparing ventilation guidelines. Ventilators are set to a low tidal volume (6 mL/kg predicted body weight) to minimize barotrauma. The resultant hypercapnia is ignored, unless associated acid-base imbalances are severe enough to threaten basic metabolic functions.^{6,8} Positive end-expiratory pressure (PEEP) is kept relatively high (often 12–15 mmHg) to maintain alveolar recruitment.⁹ FiO₂ is minimized. These settings are varied according to clinical intensive care targets that include maintaining PaO₂ 55–80 mmHg or SaO₂ 88–95%, peak inspiratory pressures less than 30 cm H₂O, and pH between 7.30 and 7.45.⁶ Utilizing these new protective ventilator settings, survival to discharge has increased from ~50% to 76%. The remaining 24% mortality rate is still undoubtedly grave.⁹

Although the diagnosis, treatment, and prognosis of ARDS are well known, there is no clear mechanism for the development of ARDS in this case. RF ablation of a pulmonary metastasis has been performed thousands of times without prior report of severe acute lung injury. Sepsis and pneumonia are the most common causes of ARDS.⁶ Both considerations are unlikely in this patient. Although the patient did report mild upper respiratory infection symptoms for 4 days prior to the procedure, the patient's blood and respiratory washings were extensively cultured for bacteria, fungi, and mycobacteria, without growing out a pathogen. The patient never mounted a white cell response to infection, although a normal marrow response may have been blunted by her prior chemotherapy, even despite holding therapy for 3 weeks prior to the procedure.

There is a known connection between subclinical interstitial pneumonia and the development of ARDS, described previously in patients undergoing pulmonary resection. The finding of interstitial pneumonia on pathology raises the risk of ARDS by an odds ratio of 6.9.¹⁰ However, in patients with increased risk of ARDS in that surgical series, bacteria were observed following microscopic sectioning of the patient's explant or at autopsy. No bacteria were seen on microscopy at the autopsy of our patient. The possibility that a patchy infection was missed secondary to sampling error is not excluded.

The most likely mechanism that could have led to ARDS in this case is aspiration. Objectively, the patient was at low risk of aspiration during this planned, elective procedure without reported complication during initial intubation. Nonetheless, all patients undergoing intubation are at risk of aspiration. The rate of aspiration of all patients undergoing general anesthesia is 1.5–5 in 10,000.¹¹ The rapid development of bilateral alveolar infiltrates on radiography could have represented pneumonitis secondary to aspiration of gastric contents. The time course in this case, progressive hypoxic respiratory failure over days, differs from classic Mendelson

syndrome of massive aspiration. Patients with massive aspiration typically experience immediate (<1 hour) development of acute, severe respiratory distress. Although inconsistent with massive aspiration, the 3-day course of progressive respiratory failure could have represented progressive pneumonitis following an initial aspiration event.

Another well-known mechanism in the development of ARDS that likely contributed to this case is pulmonary hemorrhage. Bronchial-alveolar lavage 3 days after the RF ablation procedure demonstrated RBCs in sufficient numbers to suggest alveolar hemorrhage. As suggested by the clinical team at the time, this finding of hemorrhage without gross hemoptysis may have been secondary to an initial insult, such as aspiration. Alternatively, the hemorrhage may have been secondary to barotrauma from mechanical ventilation of stiff lungs in ARDS. Another possible source of pulmonary hemorrhage would be direct bronchial injury during RF ablation. The target 4.1 cm tumor appeared to abut without invading the left hilar vessels and major bronchi on the preoperative CT. Direct injury to a hilar vessel such that it communicated with the airway is unlikely because there was no evidence of massive hemorrhage or hemoptysis.

The surgical and anesthesia literature describes ARDS as a known complication of thoracic surgery. ARDS in such patients is usually without identifiable cause, occurring in 2–4% of pneumonectomies, 1% of lobectomies, and 0.1–0.2% of thoracoscopic surgeries.¹² Surgical patients develop ARDS, on average, 4.2 days after surgery, such as in our case.¹¹ That radiographic evidence precedes the clinical signs of severe hypoxic respiratory failure is well known in such patients. ARDS has been reported following resection of a metastatic hepatic lesion. Brenner et al describe a patient with breast cancer, which was initially treated with primary resection and adjuvant chemotherapy. The patient relapsed within a year and underwent multiple additional chemotherapy regimens as well as radiation therapy for mediastinal metastases. Five years after diagnosis, the patient was suffering from refractory hepatic metastatic disease and was referred for palliative hemi-hepatectomy. The critical difference in their case from ours was the onset of respiratory failure during the hepatic resection and the ultimate recovery of their patient from ARDS. They proposed multiple possible mechanisms that could have led to respiratory failure: endotracheal tube displacement, aspiration, pulmonary embolism, cardiac ischemia with resultant pulmonary edema, transfusion associated lung injury (1:2000–5000 patients receiving plasma may have acute lung injury related to donor-specific antibodies, however, our patient did not receive a transfusion prior to ARDS development), sepsis, pneumonia, respiratory burst, and tumor-associated cytokine storm.¹³ These last two possibilities are worth further discussion in our case.

Respiratory burst refers to an increased incidence and severity of pneumonitis, which can progress to ARDS, in patients who have been presensitized to pulmonary inflammation. Common sensitizing agents include chemotherapeutic agents that damage the lungs, classically bleomycin among many others. The chemotherapeutic agents our patient received included bevacizumab, irinotecan, and oxaliplatin, none of which have frequently reported pulmonary toxicity. There is a low incidence of pulmonary fibrosis, only rarely reported a few times, in patients receiving oxaliplatin.¹⁴ There is no way to disprove preexisting pneumonitis in this case, but it is unlikely to have been the major cause of ARDS. Increased caution in patients undergoing pulmonary RF ablation may be indicated in patients with significant prior administration of agents with pulmonary toxicity. Of note, this phenomena correlates with the surgical literature that suggests an increased incidence of ARDS following pneumonectomy in patients with poor preoperative pulmonary function.¹¹ Pulmonary function tests may be an objective measurement of preprocedural risk of pulmonary complications including ARDS.

Cytokine storm is a condition that overlaps with the better-defined systemic inflammatory response syndrome (SIRS). SIRS is diagnosed when two or more of the following are present: impaired temperature autoregulation (temperature $< 36^{\circ}\text{C}$ or $> 38^{\circ}\text{C}$), tachycardia (> 90 bpm), tachypnea (> 20 respirations/minute), and leukopenia, leukocytosis or bandemia (total leukocyte counts $< 4,000$ or $> 12,000$ or immature neutrophils $> 10\%$).¹⁶ Patients with SIRS often also suffer from hypotension. Variable end organ damage can occur, including ischemia and/or failure. SIRS may have a prominent pulmonary component indistinguishable from ARDS. SIRS with ARDS-like pulmonary change has been described previously during (intraoperatively) or immediately following surgical manipulation of a large tumor.¹⁵ Increased inflammatory markers such as TNF- α and multiple cytokines have been shown to increase during tumor resection and are thought to contribute to this rare event. The contribution of cytokine release related to tumor ablation is unlikely a primary cause of ARDS in our case due to the lack of systemic SIRS, suggesting that there was no significant systemic release of proinflammatory cytokines. However, a local release of cytokines into the pulmonary vasculature could have been the initial insult to the pulmonary vascular epithelium that led to the immediate bilateral infiltrates on chest radiography. Such a release could have progressed from a local vascular injury to ARDS along the same, still-to-be-well-elicited pathways that lead from the known common causes of acute lung injury to ARDS. The probability of cytokine release into the pulmonary arterial system without significant release into the pulmonary venous system, where it would have had systemic effects, must be improbably low but

perhaps increased relative to a typical pulmonary RF ablation procedure due to the hilar location of the mass in this patient.

CONCLUSION

Pulmonary RF ablation is a well-tolerated, safe procedure in most patients. Although minor complications including pneumothorax are common, major complications are not. The development of ARDS following the ablation of a left hilar mass in our patient was a devastating complication that led to our patient's early demise. Diagnosis of ARDS is difficult initially, due to the fairly common clinical picture of hypoxic respiratory failure with pulmonary infiltrates. ARDS is well defined and easily identified once established. Therapy is supportive and low-tidal volume techniques offer decreased barotrauma and improved survival. Other adjunct therapy is under investigation, but not broadly recommended.

The mechanism by which our patient developed ARDS is unclear. Sepsis and shock, though common causes of ARDS in general, do not seem likely to apply in this case. Aspiration related to anesthesia, with a small amount of secondary alveolar hemorrhage, is the most likely cause. Other causes, including subclinical infection, pulmonary vascular cytokine release, or preexisting subclinical pneumonitis from prior chemotherapy are rare but potential contributors to ARDS in this case.

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