Extensive Diffuse Pulmonary Ossification

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Diffuse lung injury can either heal normally or progress to fibrosis. Calcification in the setting of fibrosis is common. The appearance of mature woven bone is not. We report a patient with extensive diffuse pulmonary ossification and discuss some of the theories relating to the development of this phenomenon. (Chest 1992; 102:1614-15)

Metaplastic pulmonary ossification is usually described as dendriform or nodular in patients with chronic inflammatory lung disease or long-standing pulmonary edema. We present the case of a young woman who sustained a severe pulmonary insult and was found at autopsy to have extensive immature bone formation throughout both lungs.

CASE REPORT

This 40-yr-old woman was admitted for elective laser excision of tracheal stenosis after an emergent tracheostomy one year previously for critical tracheal stenosis. Twelve years before this admission, she had had Hodgkin's disease localized in the right side of the neck treated with chemotherapy, local external radiation therapy, and a right-sided neck dissection with a tracheostomy.

Postoperative nausea and vomiting were treated with prochlorperazine. The patient developed acute dystonia that was treated with diphenhydramine. On the third postoperative day, she had a generalized seizure. Her postictal laboratory values included a serum sodium of 116 mEq/L, potassium of 5.0 mEq/L, chloride of 90 mEq/L, bicarbonate of 10 mEq/L, and normal renal function.

Later, the patient was hypotensive and in respiratory distress with decorticate posturing. An emergent computerized tomogram of the head showed mild hydrocephalus.

In the medical intensive care unit (ICU), a bedside ventriculostomy was placed, and normal intracranial pressure was recorded. The patient was maintained on mechanical ventilation and intravenous pressures while her electrolyte levels were corrected, and she woke up within 48 h. Antibiotics were begun after a chest roentgenogram showed bilateral infiltrates consistent with aspiration pneumonia. The infiltrates began to clear but soon worsened in association with low pulmonary capillary wedge pressures and negative cultures and stains from bronchoscopic specimens and blood. The patient was diagnosed as having adult respiratory distress syndrome.

Oxygenation became more difficult as pulmonary compliance dropped. The patient had to be sedated and paralyzed while inverse-ratio ventilation was initiated. Oxygenation and ventilation continued to worsen on high levels of positive end-expiratory pressure and a prolonged toxic fraction of inspired oxygen. On the 26th day in the ICU, failing hemodynamics and persistent bilateral bronchopleural fistulas prompted the institution of high-frequency jet ventilation (Fig 1). On the 36th day in the ICU, the patient died.

Permission was granted for a complete autopsy. The lungs, which weighed 2,180 g together, were diffusely firm with patchy hard tan regions that were scattered throughout all lobes and measured up to 5 cm. Microscopically, the lung architecture was severely distorted by organizing interstitial fibrosis overlaid with large regions of partially calcified woven (immature) bone. The bone had numerous osteoclasts and was associated with osteoclastic and prominent osteoblastic activity (Fig 2). No separate calcification was found. Additional findings at autopsy included acute pancreatitis, adrenal cortical necrosis, nonbacterial thrombotic endocarditis, multiple visceral infarcts, and tracheal stenosis.

DISCUSSION

Metaplastic pulmonary ossification is usually discovered at autopsy in the setting of other pulmonary injury. Two types of diffuse or disseminated ossification are described: (1) dendriform, with its characteristic branching along terminal airways and occasional islands of marrow; and (2) nodular, which tends to be more circumscribed and situated

![Figure 1. Chest roentgenogram taken with portable technique, illustrating diffuse bilateral alveolar infiltrates, bilateral pneumothoraces with thoracostomy tubes, and right heart catheter in place.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21658/ on 06/21/2017)
in alveolar spaces. Each is composed of mature lamellar bone with little osteoblastic or osteoclastic activity and no separate ossification. They appear mostly in the lower lobes of patients who are male, in their fifth to sixth decade, and have a history of repeated pulmonary insults such as recurrent bronchopneumonia, anthracosis, interstitial fibrosis, and pulmonary edema, particularly with mitral stenosis. Chest roentgenograms show either "branching shadows of calcific density (dendriform type) extending along the bronchovascular distribution," commonly interpreted as scarring, fibrosis, or bronchiectasis; or multiple subpleural calcifications (nodular type), less than 1 cm, mimicking healed infectious disease.2

Generation of bone tissue in lung is not necessarily an irreversible clinical phenomenon. Cases have been reported where lung biopsies taken during an acute but prolonged illness showed bone formation, but the patient recovered clinically. No data are available in these cases as to whether the roentgenographic or histologic changes reversed.3

Pulmonary ossification has been related to both experimentally induced bone formation and embryologic bone development. The ability of in vitro rat bone matrix to promote transformation of cultured fibroblasts into osteoblasts is affected by the ionic charge.1 Inflammation, tissue anoxia, and shock may promote this transformation in vivo.4 Stress forces normally shape healing or growing bone, possibly by depressing intracellular levels of cyclic AMP and cyclic GMP, thereby stimulating cell proliferation and growth.5 Shear stresses associated with poorly compliant lung tissue may induce fibroblast and osteocyte formation. Furthermore, fibrin, platelets, and fibroblasts interact in the acutely injured alveolus,6 in an acid milieu that is known to enhance the production of collagen,7 contributing to the formation of bone matrix and the appearance of osteoblasts.

Transforming growth factor-β (TGF-β) elaborated by inflammatory cells plays a role in embryonal organogenesis, tissue regeneration, fibrosis, and the formation of extracellular matrix;8 TGF-β strongly stimulates the biosynthesis of type 1 collagen, fibronectin, proteoglycans, and protease inhibitors while inhibiting the expression of proteases.9 The gene for TGF-β shares sequence homology with that for bone morphogenetic protein (BMP).10 TGF-β and BMP genes expressed at a site of inflammation would promote fibrosis and metaplastic bone formation, instead of healing.

The patient described herein sustained several insults that could potentiate pulmonary fibrosis and then ossification: chemotherapy, external radiation, chronic asphyxia, shock, prolonged high levels of inspired oxygen, and prolonged high-pressure and high-frequency ventilation. In this case, extensive immature bone formation occurred in a setting of proliferative interstitial fibrosis, probably representing an organizing phase of a recent diffuse pulmonary insult such as diffuse alveolar damage. A similar type of osseous metaplasia has been described in proliferating connective tissue within a pulmonary adenocarcinoma.11 Our patient is distinctly unusual for the type and extent of pulmonary ossification that contributed to her respiratory failure.

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