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Unusual progression and subsequent improvement in cystic lung disease in a child with radiation-induced lung injury

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Abstract

Radiation-induced lung disease is a known complication of therapeutic lung irradiation, but the features have not been well described in children. We report the clinical, radiologic and histologic features of interstitial lung disease (ILD) in a 4-year-old child who had previously received lung irradiation as part of successful treatment for metastatic Wilms tumor. Her radiologic abnormalities and clinical symptoms developed in an indolent manner. Clinical improvement gradually occurred with corticosteroid therapy. However, the observed radiologic progression from interstitial and reticulonodular opacities to diffuse cystic lung disease, with subsequent improvement, is striking and has not been previously described in children.

Keywords

Cystic lung disease; Radiation pneumonitis; Lung biopsy; Interstitial lung disease; Wilms tumor; Child

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Conflicts of interest: None

Introduction

Radiation-induced pneumonitis is a form of interstitial lung disease (ILD) associated with therapeutic irradiation. Abnormal radiologic or pulmonary function findings are seen in thirty percent of patients who receive lung irradiation and are associated with increased pulmonary morbidity and mortality [1]. Limited data are available regarding the features and outcomes of radiation-induced pneumonitis in children.

Case report

A 33-month-old girl presenting with constipation and abdominal distention was found to have bilateral renal masses. Staging evaluations and surgical biopsy confirmed stage V anaplastic Wilms tumor with hepatic and numerous pulmonary metastases. She was successfully treated with resection of renal and hepatic foci, chemotherapy (vincristine, actinomycin-D, doxorubicin, carboplatin, cyclophosphamide and etoposide), and whole lung and abdomen irradiation (1,200 cGy whole lung, 1,050 cGy whole abdomen, and 1,950 cGy whole liver) per the institutional standard of care.

Six months after completing chemotherapy and 10 months after radiation therapy, she presented with shortness of breath and worsening of chronic dry cough. In retrospect, these symptoms had been gradually progressive over the prior 4 months. A chest radiograph showed diffuse bilateral coarse interstitial opacities throughout both lungs with a mild nodular component (Fig. 1). A chest CT demonstrated extensive micronodular parenchymal opacities throughout both lungs, greatest in the lung bases. Diffuse interlobular septal thickening, ground glass opacities, pneumomediastinum and innumerable diffusely scattered thin-walled lung cysts were also present (Fig. 1). These radiologic findings were new as compared to a surveillance CT scan performed 3 months prior (not shown). Extensive infectious evaluations including flexible bronchoscopy and testing for *Pneumocystis jirovecii* pneumonia were negative. Bronchoalveolar lavage cytology was mildly inflammatory with 55% macrophages, 29% lymphocytes, and 16% neutrophils. No mutations were identified in sequencing of the genes encoding surfactant protein C (*SFTPC*) and ATP-binding cassette member A-3 (*ABCA3*), which have been associated with ILD in children. An overnight oximetry study and 6-min walk test revealed hypoxemia with sleep and exercise, and supplemental oxygen was started. An echocardiogram was normal. Pulmonary function testing (spirometry) was attempted, but the results were not reproducible due to patient technique and cooperation.

Based on the imaging findings and clinical context, a presumptive diagnosis of radiation pneumonitis was made. Empiric therapies of prednisolone (2 mg/kg/day) and azithromycin (3 days/week) were initiated. She gradually improved clinically, with resolution of resting tachypnea and exercise-induced desaturation. Mild hypoxemia with sleep persisted. Three months later, a repeat chest CT showed reduction in the micronodular opacities, but instead marked interval progression in the size and number of thin-walled cysts present throughout both lungs with ground glass opacity present between the cystic spaces (Fig.1). Based on her clinical response, the corticosteroid dose was gradually tapered over several months, with ongoing clinical stability and successful discontinuation of supplemental oxygen.

However, upon more accelerated tapering of oral corticosteroids, she again developed chronic cough and supplemental oxygen requirement. Flexible bronchoscopy was normal with non-inflammatory bronchoalveolar lavage cytology. Her chest CT demonstrated persistent but improved mild diffuse ground glass attenuation and improvement in the overall number and size of thin-walled cystic lesions (Fig. 1). A lung biopsy was performed via video-assisted thoracoscopic surgery to help guide the approach to further immunomodulatory therapy. Histologic findings were consistent with radiation-induced lung injury (Fig. 2), including interstitial inflammation and fibrosis. There was no evidence of acute infection or malignancy. As fibrosis was the most prominent finding, with only mild inflammation present, gradual corticosteroid tapering was resumed and was ultimately well-tolerated. The patient is currently asymptomatic, without exercise intolerance or supplemental oxygen requirement, and the cystic component of her lung disease has continued to regress (Fig. 3).

Discussion

Diffuse cystic lung disease is rare in children, presenting a challenging radiologic differential. Etiological considerations for cystic lung disease in children include Langerhans cell histiocytosis, lymphocytic interstitial pneumonia often in conjunction with immunodeficiency syndromes, *SFTPC* gene mutations, lung developmental disorders including in association with Trisomy 21 or *NKX2-1/TTF1* gene mutations, or more focal cystic lesions in association with congenital lesions or post-infectious processes [2]. Other causes of multiple cystic lung disease predominantly described in adults include lymphangioleiomyomatosis and tuberous sclerosis complex, Birt-Hogg-Dube syndrome, Sjogren syndrome, light-chain deposition disease and, rarely, metastasizing tumors [3]. This case of radiation-induced lung disease represents a cause of cystic lung disease not previously reported in children. Further, the extent of radiologic improvement in this case was unexpected, illustrating that cystic change may not simply reflect permanent lung destruction and thus may be potentially reversible, depending on the context.

Many causes of cystic lung disease in both children and adults are associated with poor prognosis, but the natural history is variable, largely related to the underlying causative condition. Mechanisms of lung cyst formation have been attributed to parenchymal lung destruction but may also occur due to small airway obstruction. While our patient was followed by CT imaging due to her age and need for oncological surveillance, pulmonary function testing is the primary method of monitoring disease activity in most patients with cystic lung disease. Pulmonary function testing in such patients may demonstrate obstructive physiology with evidence of air-trapping, as seen by an elevated residual volume. Due to her very young age, our patient was not able to perform acceptable and reproducible spirometry or plethysmography for assessment of lung volumes.

Wilms tumor is the most common primary renal malignancy in children, with an overall survival rate of up to 90%. Lung radiotherapy for pulmonary metastases has been associated with a 4.8% prevalence of lung disease within 15 years [4]. This patient's serial chest imaging, obtained as part of her Wilms tumor follow-up protocol, provided a unique opportunity to observe the progression of her radiation-induced lung disease. The shift from

interstitial and reticulonodular abnormalities to marked cystic changes, with subsequent improvement, is striking and has not previously been described in children, to the best of our knowledge. While a spectrum of abnormal radiologic findings has been reported in adults who have received direct or indirect lung irradiation for treatment of malignancies, only more limited data are available regarding the features and outcomes of radiation-induced pneumonitis in children.

The mechanisms of radiation pneumonitis include alveolar epithelial cell injury from DNA damage and free radical generation from ionizing particles. Ultimately, fibrosis results from proliferation of fibroblasts and myofibroblasts and extracellular matrix deposition in response to injury. A subacute pneumonitis typically develops 4-12 weeks following irradiation, with fibrotic changes seen after 6-12 months. The extent of disease partially relates to cumulative radiation dose, volume of lung tissue irradiated and age, with younger children being more susceptible [5]. However, it remains difficult to reliably predict the disease course. Corticosteroids may have utility in treating early inflammatory stages of radiation pneumonitis, but there are no controlled trials or evidence of efficacy in treating established fibrosis [6].

Often the cause of pneumonitis in children is difficult to prove with certainty. Indeed many chemotherapeutic agents have been associated with radiation-induced lung injury, though such recall injuries correlate unpredictably with radiation dose and chemotherapy received. Cyclophosphamide, which our patient received subsequent to radiation, can cause several types of direct lung injury, including diffuse alveolar damage and fibrosis [7]. Further, anthracyclines such as doxorubicin administered subsequent to radiotherapy have been linked to pneumonitis in mice and in patients [8]. Our patient received doxorubicin at intervals and doses comparable to those described in these reports. What remains unique about our patient's case is the relatively late timing of her respiratory symptoms and radiologic changes, as chemotherapy-induced lung damage is most often seen concurrently with administration of the offending agent.

In summary, this case reports a pattern and evolution of imaging findings not previously described in association with radiation-induced lung injury in a child. This case also serves as a reminder of the potential for a discrepant timeline between clinical outcomes and imaging findings, and thus emphasizes the importance of integrating imaging findings with physiological and functional measures in assessing the treatment response in children with diffuse lung diseases. Ultimately, improved understanding of the mechanisms governing progression and resolution of lung injury including in cystic lung diseases may have broad implications for many forms of lung disease in both children and adults.

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References

1. Weiner DJ, Maity A, Carlson CA, et al. Pulmonary function abnormalities in children treated with whole lung irradiation. *Pediatr Blood Cancer*. 2006; 46:222–227. [PubMed: 15926160]
2. Guillerman RP, Brody AS. Contemporary perspectives on pediatric diffuse lung disease. *Radiol Clin North Am*. 2011; 49:847–868. [PubMed: 21889012]
3. Seaman DM, Meyer CA, Gilman MD, et al. Diffuse cystic lung disease at high-resolution CT. *AJR Am J Roentgenol*. 2011; 196:1305–1311. [PubMed: 21606293]
4. Sasso G, Greco N, Murino P, et al. Late toxicity in Wilms tumor patients treated with radiotherapy at 15 years of median follow-up. *J Pediatr Hematol Oncol*. 2010; 32:e264–267. [PubMed: 20736847]
5. Green DM, Lange JM, Qu A, et al. Pulmonary disease after treatment for Wilms tumor: a report from the national wilms tumor long-term follow-up study. *Pediatr Blood Cancer*. 2013; 60:1721–1726. [PubMed: 23776163]
6. Abratt RP, Morgan GW, Silvestri G, et al. Pulmonary complications of radiation therapy. *Clin Chest Med*. 2004; 25:167–177. [PubMed: 15062608]
7. Malik SW, Myers JL, DeRemee RA, et al. Lung toxicity associated with cyclophosphamide use. Two distinct patterns. *Am J Respir Crit Care Med*. 1996; 154:1851–1856. [PubMed: 8970380]
8. Prestwich RJ, Picton SV, Glaser A, et al. Fatal pneumonitis in children with metastatic rhabdomyosarcoma following whole lung radiotherapy and sequential epirubicin. *Pediatr Blood Cancer*. 2007; 48:586–590. [PubMed: 16302221]

Abbreviations

<i>ABCA3</i>	gene encoding the ATP-binding cassette member A-3
<i>ILD</i>	interstitial lung disease
<i>NKX2-1/TTF1</i>	gene encoding the thyroid transcription factor-1
<i>SFTPC</i>	gene encoding surfactant protein C

Fig. 1.

Serial radiologic findings during course of oncological surveillance reveal an evolution of diffuse ground-glass micronodular opacities, septal thickening, and lung cysts over time. **a-b** Chest radiographs performed at age 4 years, 1 month, when the patient presented with shortness of breath and cough. Findings include diffuse bilateral coarse interstitial opacities throughout both lungs with a mild nodular component. **c-d** Chest CT images at age 4 years, 1 month show extensive micronodular parenchymal opacities throughout both lungs, which were greatest in the lung bases. Diffuse interlobular septal thickening, ground glass opacities, pneumomediastinum and innumerable diffusely scattered lung cysts were also noted. These findings were new compared to a prior oncological surveillance chest CT done 3 months prior. **e-f** Chest CT images at age 4 years, 4 months reveal marked reduction in the micronodular opacities but instead striking interval progression in the size and number of thin-walled cysts present throughout both lungs. Ground glass opacity persists between the cystic spaces. **g-h** Chest CT images at age 4 years, 10 months demonstrate persistent but improved mild diffuse ground glass attenuation and interlobular septal thickening, with improvement in the overall number and size of thin-walled cystic lesions. However, due to clinical deterioration upon steroid weaning, the decision was made to proceed to diagnostic lung biopsy at this time

Fig. 2.

Lung histopathology at age 4 years, 10 months demonstrates findings consistent with radiation-induced lung injury. **a** A region of alveolar sampling demonstrates findings of mild interstitial inflammation and fibrosis, with increased macrophages present (20×). Macrophages were hemosiderin positive indicating prior pulmonary hemorrhage (not shown). Arrows denote a region best illustrating the interstitial expansion. **b** Irregular focus of dense fibrosis in the lung parenchyma (*asterisk*) with a mixed cellular infiltrate (10×). **c-d** Subpleural cystic remodeling and peri-cystic fibrosis (4×). Asterisk denotes a cystic area

Fig. 3. Chest CT images at age 6 years, 4 months demonstrate ground glass opacity and mild interlobular septal thickening, but findings are improved compared to prior imaging. In addition, the number and size of subpleural and intraparenchymal thin-walled cysts have continued to decrease