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Does This Chest Radiograph Belong to a Survivor of Childhood Cancer?
Radiographic Findings Suggesting Previous Treatment for Childhood Cancer – A Review

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Introduction

Advances in the detection, treatment, and supportive care of pediatric malignancies has allowed for improved long-term survival among childhood cancer survivors. At present, the 5-year survival for those diagnosed with a pediatric malignancy exceeds 80% with a 10-year survival rate of 75%. The increasing number of adult survivors of childhood malignancies now approaches an estimated 360,000 individuals, allowing for more extensive studies of the delayed manifestations of adverse effects related to cancer treatment. Medical conditions that persist or present in 5 or more years following treatment are referred to as late effects. Studies that investigate the late effects of pediatric cancer treatment have shown that 73.4% of survivors will experience a chronic medical condition, with over 40% experiencing a serious or life-threatening problem.

The manifestations of late effects are wide ranging and involve all organ systems, with differential presentation largely dependent on both the primary malignancy and the treatment received. Some of the most common late effects observed in childhood cancer survivors are pulmonary and cardiac complications, with skeletal complications and secondary malignancies being less common. The increased survivorship and incidence of morbidity amongst those treated for childhood malignancies necessitates increased vigilance on the part of the adult survivors’ health-care providers to both detect and treat the anticipatory late effects in this population. The manifestations of tissue injury from therapy administered during childhood may not become apparent until the patient enters a phase of rapid growth, such as adolescence. At such times, the treatment insult on normal tissues may result in impaired growth. Diagnostic imaging can provide a robust means through which many late effects can be detected.

The aim of this article is to provide an overview of selected radiographic manifestations of thoracic findings that may be associated with previous treatment for pediatric cancers and their late effects by providing an image-based approach to identifying unique radiographic characteristics that may be seen on chest radiographs obtained for reasons unrelated to a history of previous childhood cancer. The risk factors for and prevalence of tumor recurrence and secondary malignant neoplasms are well-described in the literature and will not be included in this pictorial review.

Residual Mediastinal Mass After Treatment For Lymphoma

The presence of residual abnormality of the mediastinum or hila after completion of therapy for lymphoma can induce anxiety in patients, parents, and healthcare providers. Approximately two-thirds of patients with Hodgkin lymphoma and one-third of patients with non-Hodgkin lymphoma have been reported to have residual mediastinal masses after completion of therapy, which can be apparent on chest radiographs (Fig. 1). These residual masses more often occur in patients presenting with bulky mediastinal disease or those with nodular sclerosing subtype of Hodgkin disease. The residual soft tissue masses are usually composed of benign fibrotic or inflammatory tissue and may be seen in up to 41% of chest radiographs and 46% of chest CTs in pediatric patients treated for Hodgkin disease; these masses may calcify (Fig. 2). Typically, residual fibrotic masses continue to regress over time.

Particularly in pediatric patients, thymic rebound, developing after completion of therapy, may mimic a residual mass. Comparison with prior chest imaging can resolve whether or not the original mass has
changed in size and contour. Increase in the residual mass or new adenopathy warrants further evaluation for the possibility of recurrent disease (Fig. 3). Such can be accomplished using MR\textsuperscript{10,11} or CT for anatomic characterization of changes seen on chest radiographs.\textsuperscript{6} However, MR and CT have limited ability to differentiate between active disease and fibrosis or scarring.\textsuperscript{9-13} Thus, 18F-FDG PET/PET-CT may be used to assess for metabolic activity (having largely replaced \textsuperscript{67}Gallium imaging) that may indicate disease relapse.\textsuperscript{6,13}

**Pulmonary Complications**

The lungs are one of the most radiation- and chemosensitive organs in the body.\textsuperscript{14} Functional compromise arising from radiation is compounded by chemotherapy-induced toxicities, all of which may progress from initial injury to the pulmonary interstitium to pulmonary fibrosis over time.\textsuperscript{14} Pulmonary complications after therapy for childhood cancer include pulmonary fibrosis (Fig. 4), chronic cough, recurrent pneumonia, requirement for supplemental oxygen, and pleurisy. Mertens, et al. reporting on the prevalence of self-reported pulmonary complications from the Childhood Cancer Survivor Study, found that chest radiation was statistically associated with all of these adverse late effects, as were various chemotherapeutic agents.\textsuperscript{14} Chemotherapeutic agents associated with development of pulmonary insufficiency include busulfan, carmustine\textsuperscript{14,15}, cyclophosphamide, lomustine, and bleomycin.\textsuperscript{15} At 20 years from diagnosis of the primary malignancy, a 3.5% cumulative incidence of pulmonary fibrosis was
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Figure 3. Relapse Lymphoma.
9-year-old boy diagnosed with Stage IA Hodgkin disease right neck achieved complete remission with chemotherapy. At routine follow-up 3.5 years later, left hilar relapse was suspected. Posteroanterior (A) and lateral (B) chest radiographs show stable post-therapy appearance of the thoracic structures. Follow-up posteroanterior chest radiograph (C) shows slight increased density left hilum which, on the lateral view (D), is shown to represent an ovoid nodule (lines). Axial non-contrast T1 (E) and T2 (F) weighted MR images of the chest show right paratracheal (long arrows), left hilar and subcarinal (short arrows) adenopathy, consistent with disease relapse.

Figure 4. Progressive Radiation Fibrosis.
19-year-old woman diagnosed with Stage IIA nodular sclerosing Hodgkin disease was treated with chemotherapy and 2550 cGy modified mantle irradiation. One year after completing therapy, she developed disease relapse treated with intensive chemotherapy, autologous stem cell rescue, and radiation therapy to the lower cervical spine and porta hepatitis. At diagnosis, the posteroanterior chest radiograph (A) showed right paratracheal adenopathy and bilateral superior mediastinal widening, which improved with therapy. By 3 years later, posteroanterior chest radiograph (B) demonstrated straightening of the left mediastinum and early cephalad retraction of the left hilum. At 11 years, posteroanterior chest radiograph (C) showed progression of cephalad retraction of the left hilum and coarsening of post-radiation scarring. Imaging findings paralleled the patient’s decreasing pulmonary function, ultimately leading to her demise.

Radiographic findings of fibrosis include pleural thickening, regional or focal pulmonary contraction, linear scarring, and streaking that may extend beyond the distribution of radiation portals. The likelihood and severity of development of pulmonary complications is dependent on the dose of radiation and chemotherapy, younger patient age at the time of therapy, and smoking. Pulmonary function longitudinally declines after therapy and may compound the decrease in pulmonary function normally seen with aging. Further, chemotherapy, surgery, and bone marrow transplantation may compound the effects of radiation therapy.

Cardiomyopathy

An increased risk for cardiovascular disease is seen in survivors of childhood cancer treated with radiation therapy or chemotherapy, independently or in combination, and represents a cause of cardiac morbidity and mortality. Risk factors particularly identified to increase the likelihood of developing anthracycline-associated cardiovascular toxicity include age younger than 5 years at the time of treatment, female sex, cumulative doses of 300 mg/m$^2$ or greater, cardiac irradiation of 3000 cGy or more, and chemotherapy combined with radiation therapy. In addition, Orgel, et al. recently reported that an elevated body mass index and Hispanic ethnicity are also independent risk factors for the development of declining left ventricular shortening fraction in anthracycline-based therapy for acute
myeloid leukemia.\textsuperscript{24} Other reported risk factors include black race and the presence of trisomy 21.\textsuperscript{25}

The most common cardiac event reported is congestive heart failure.\textsuperscript{26} The hallmark of anthracycline cardiotoxicity is reduced thickness and mass of the left ventricular wall.\textsuperscript{27} Though symptomatic cardiac compromise is infrequent\textsuperscript{22,23}, a recent study reported a 12.6\% incidence of such events in patients treated with both anthracyclines and cardiac irradiation, 7.3\% incidence with anthracyclines alone, and 4.0\% incidence after cardiac irradiation with a median patient age of 27 years at the time of the events\textsuperscript{26} (Fig. 5). Cardiotoxic effects of therapy may not manifest until adulthood or during times of stress, such as pregnancy or physical exertion.\textsuperscript{22}

A recent investigation of 62 adolescent survivors of childhood cancer (mean age 14.6 years at the time of study) who received anthracyclines as part of their oncotherapy found that gadolinium-enhanced cardiac MR detected and quantified both left and right ventricular dysfunction in 61\% and 27\%, respectively.\textsuperscript{28}

Breast Hypoplasia

Breast hypoplasia or aplasia is a well-known late effect following irradiation to the chest during childhood (Fig. 6). Radiation-induced underdevelopment of the breast has been reported in a variety of pathologies for which irradiation has been used, including cutaneous hemangiomas of the chest,\textsuperscript{29} mediastinal lymphadenopathy,\textsuperscript{30} Wilm tumor,\textsuperscript{31, 32} and neuroblastoma.\textsuperscript{32} Radiation effects on developing human breast tissue is dose dependent\textsuperscript{30, 33} and may occur with doses of <\textasciitilde{}500 cGy.\textsuperscript{34} Clinical changes associated with radiation-induced breast underdevelopment include the presence of dyschromasia and telangiectasias on the affected breast, as well as overall asymmetric breast development with the irradiated breast being smaller and irregular in size compared to the non-irradiated breast.\textsuperscript{33} Reported histopathological findings of irradiated hypoplastic breasts include extensive fibrosis, loss of breast lobules, and significant shrinkage of the ducts.\textsuperscript{33} Patients affected by breast hypoplasia can also experience significant psychological distress due to the undesirable cosmetic effects of asynchronous breast growth.\textsuperscript{33}

It is important to recognize the association of breast cancer arising as a result of irradiation that included

![Figure 5. Anthracycline-induced Cardiomyopathy.](image)

12-year-old patient diagnosed with nodular sclerosing Hodgkin disease and received multiagent chemotherapy that included anthracycline. Pathologic examination revealed Grade 2 of 3 anthracycline cardiac toxicity. Posteroanterior chest radiograph obtained about 1 year after completion of therapy demonstrates cardiomegaly, bilateral pleural effusions, and pulmonary vascular congestion indicative of congestive heart failure.

![Figure 6. Breast Hypoplasia.](image)

49-year-old woman diagnosed with Wilm tumor at 5 years of age and received 1200 cGy whole lung irradiation for pulmonary metastases, as well as 1200cGy abdominal radiation therapy for primary disease and hepatic metastases. Posteroanterior (A) and lateral (B) chest radiographs demonstrate hypoplasia of both breasts. The anteroposterior diameter of the chest is narrow from radiation-induced rib dysplasia.
hypoplasia of bones exposed to radiation therapy, demineralization associated with chemotherapy and/or radiation therapy, growth aberrations related to radiation therapy, and altered vertebral height when radiation therapy is compounded by the effects of chemotherapy. Similarly, chemotherapy can directly affect growing bones. Growing bone is most susceptible to the effects of radiation during the two periods of most rapid growth: during the first 6 years of life and during puberty. Radiation injury is most likely related to injury of chondroblasts with inhibition of cartilaginous cells and is seen with single doses of 200 to 2000 cGy. Thus, the adverse impact of treatment—whether chemotherapy, radiation therapy, or in combination—on the developing skeletal structures varies with patient age, as well as the type, distribution, and intensity of therapy at the time of treatment.

Scoliosis

Impaired vertebral growth can occur with doses of 1000 to 2000 cGy and can lead to short stature, altered vertebral body configuration, and contribute to the development of scoliosis and/or kyphosis (Figs. 7 and 8). Probert and Parker reported changes in developing vertebral bodies when exposed to radiation doses of greater than 2000 cGy. Asymmetric exposure of the vertebral bodies may contribute to the development of scoliosis.

In addition to therapeutic irradiation, chest wall resection may result in scoliosis. In children, postsurgical scoliosis is progressive and related to the number of posterior ribs resected.

Clavicular Growth

Merchant, et al. investigated the effect of asymmetric exposure of the clavicles to 1500 cGy as administered with hemi-mini-mantle irradiation for unilateral Hodgkin disease of the neck or supraclavicular region. The clavicles which were fully exposed to radiation therapy grew 0.5 cm less overall compared to those only partially exposed (p=0.007), regardless of the patient’s age at the time of therapy (median age, 13.3 years; range, 5.1 to 18.9 years).
Further, the effect on clavicular growth was more pronounced in the younger-aged patients (mean age, 9.9 years) compared to those who were older (mean age, 16.4 years; \( p=0.036 \)). Thus, as with prior reports, the effects of radiation therapy on bone are influenced by patient age, therapeutic dose, and extent of tissues exposed.

### Radiation-Induced Exostosis

Osteochondromas are the most common benign tumor of bone to occur following radiation therapy. They manifest as a late effect of total body or local irradiation and have also been reported as a long-term sequela of hematopoietic stem cell transplantation (HSCT). The median age of presentation and latency for osteochondromas following HSCT is 13.3 and 8.9 years, respectively. Among the risk factors investigated as contributing to their development following HSCT, only total body irradiation and a young age at time of TBI and or HSCT have been consistently shown to significantly affect the risk of developing osteochondromas.

The prevalence of osteochondromas is approximately 3% in the general population with the majority presenting as solitary osteochondromas unless in the setting of hereditary multiple exostosis. Among survivors of HSCT, approximately 1% develop osteochondromas. In pediatric patients who undergo irradiation, damage to the epiphyseal plate causes a portion of the epiphyseal cartilage to migrate to the metaphyseal regions.
causing the formation of osteochondromas.

Osteochondromas that occur as a result of irradiation are radiographically indistinguishable from those that occur from other etiologies. Osteochondromas most commonly localize to the metaphysis of long bones, particularly the femur and proximal tibia, with involvement of flat bones being less common. Clinically, osteochondromas present as painless slow-growing masses that cause local distortion of tissue. Depending on their proximity to neurovascular structures, osteochondromas can present with paresthesias or loss of peripheral pulse in the affected limb. In addition to the above presentations, a minority of long-term survivors of HSCT are diagnosed with osteochondromas incidentally through the course of routine radiographic or clinical examination.

Radiographically, the appearance of osteochondromas can be described as cartilage capped protruding osseous lesions that have cortical and medullary contiguity with the parent bone. The neck of an osteochondroma can either be wide or narrow, giving the appearance of either a sessile or pedunculated lesion, respectively. Osteochondromas can be easily recognized using radiographs. However, more complex lesions, such as those that involve the spine or shoulder, can be better resolved with computed tomography. Magnetic resonance imaging can accurately distinguish osteochondromas from other osseous lesions due to the contrast of high T2 and low T1 signal intensity of the cartilaginous cap.

**Demineralization**

Survivors of childhood cancer are at risk for deficits in bone mineral density which may lead to earlier onset and more severe osteoporosis and related fractures. Attention to the integrity of bone mineralization in the thoracic spine of childhood cancer survivors is important. Occasionally, compression fractures may be the first indication of such a deficit in survivors of childhood cancer. Though the best studied pediatric cancer population has been children treated for acute lymphoblastic leukemia, such deficits are associated with a variety of pediatric malignancies, as well as with bone marrow transplantation.

Deficits in bone mineralization arise from a multitude of risk factors and include genetic predisposition, lifestyle factors (such as suboptimal nutrition), inadequate weight-bearing exercise, treatment with osteotoxic chemotherapeutic agents (particularly glucocorticoids but also associated with ifosfamide and methotrexate), endocrinopathies, and radiation therapy whether localized to the thoracic spine or gonads, or cranial irradiation.

![Figure 10. Radiation-Induced Exostosis.](image)

A 7-year-old girl returned 4 years after undergoing bone marrow transplantation for chronic myelogenous leukemia because of a newly found "lump" in her right anterior chest. The preparative regimen for her bone marrow transplantation included total body irradiation. Posteroanterior chest radiograph (A) was obtained, demonstrating expansion of the right anterior seventh rib (arrow). Axial limited chest CT (B) was performed through the rib for characterization of the abnormality shown on the chest radiograph and shows the typical appearance of an exostosis (skin marker).
Children undergoing therapy for childhood cancer are at risk for osteonecrosis when treatment includes high dose glucocorticoids, bone marrow transplantation, and/or local radiation (Fig. 11). The reported prevalence of osteonecrosis in these survivors varies with the modality used to detect the toxicity (MR being the most sensitive modality), whether or not a report was based upon patients having symptoms, age at the time of diagnosis of the primary disease, and type of treatment. In contrast to the general population, osteonecrosis in survivors of childhood cancer occurs as a multijoint toxicity in 60% of those in whom it develops. As reported by the Childhood Cancer Survivor Study, the most frequent joints involved are the hips (72%), shoulders (24%) and knees (21%).

Summary

The rapidly growing population of survivors of childhood cancer underscores the need for recognizing potential sequelae of both the primary disease and associated therapies, to include knowledge of risk factors for complications. While numerous reports are available regarding second malignant neoplasms in this population, only in the more recent past have investigations and understanding of adverse toxicities manifesting after completion of therapy been undertaken. It is with the hope of enhancing care of survivors of childhood cancer that this review of the more common chest manifestations has been developed. Though not meant to be all-inclusive, this work serves as a starting point to enhance the acumen of imaging healthcare providers, and thus, improve the care of these patients.

Figure 11. Osteonecrosis.

20-year-old woman diagnosed with B-cell non-Hodgkin lymphoma at 16 years of age experienced multiple relapses of the disease. She was treated with multiagent chemotherapy that included high dose glucocorticoids. The posteroanterior chest radiograph showed changes of osteonecrosis of the left humeral head. Dedicated radiographs of the shoulders confirmed the advanced osteonecrotic changes of both humeral heads with crescent signs, collapse of the articular surfaces, and intermixed areas of sclerosis and cystic changes.

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