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Pitfalls in Oncologic Imaging: Complications of Chemotherapy and Radiotherapy in the Chest

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Introduction

Advances in cancer chemotherapy and radiation therapy continue to improve patients' lives and affect patient care. Chemotherapy has progressed from cytotoxic agents to newer targeted agents that are geared to attack specific mutations in cancer cells. The toxicities of these newer cytotoxic drugs and targeted agents have specific imaging appearances depending on the mechanism of action. Similarly, advances in radiation therapy allow for better tumor, with less effect on normal adjacent structures. Knowledge of the imaging appearance of toxicities of therapy is crucial for radiologists to accurately diagnose complications of therapy and to avoid imaging pitfalls. Radiologists must use the clinical history and the mechanism of action of the drugs to affect patient care and prevent misdiagnosis. In this article, we review some of the common pitfalls of imaging that arise because of complications of therapy.

Chemotherapy

Cytotoxic chemotherapy is based on interfering with rapidly dividing cells and interrupting DNA and RNA synthesis. These include intercalating agents such as cisplatin and the newer agent oxaliplatin. Topoisomerase inhibitors include irinotecan and topotecan. Antimetabolites include methotrexate and gemcitabine. The expected toxicities are seen in the gastrointestinal system and bone marrow, but toxicity may also be seen in other rapidly growing cells, such as in the thorax (methotrexate and gemcitabine).

The newer targeted therapies are designed to target receptors on the cell, and therefore, the toxic effects may be more widespread. The mechanism of action may be helpful in determining the toxicity. Drugs that target the vascular endothelial growth factor receptor (VEGFR) include bevacizumab, sorafenib, sunitinib, and pazopanib. Erlotinib and gefitinib target the epidermal growth factor receptor. Everolimus and temsirolimus target the mammalian target of rapamycin. Drugs targeting the transmembrane protein with tyrosine kinase (kit) receptor include imatinib and sunitinib. Rituximab targets the B-lymphocyte antigen CD20 receptor. Ipilimumab is an example of an immunomodulating agent that exerts effects on T-cell receptors. These agents may have more toxicities seen on imaging when compared with the conventional agents.

Radiation

Technology in radiation therapy has evolved to give the greatest dose to the tumor and decrease the effect on the normal tissues. The new technologies include intensity-modulated radiation therapy, stereotactic body radiation therapy, and proton therapy. Acute radiation side effects usually manifest in the first 3 months of therapy and may be a precursor for chronic radiation side effects, which typically occur after 6 months to a year.

Chemotherapy

Lung Complications

Pulmonary Toxicity

Lung toxicity due to chemotherapy may occur during the start of, during, or after many years of treatment. Risk factors include advanced age, smoking history, history of pre-existing lung disease, prior radiation, or concurrent chemotherapy and

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Table Possible Causative Agents of Pulmonary Toxicity

Bleomycin	Cytotoxic	Pulmonary Opacities	Leukemia
Paclitaxel	Cytotoxic	Ground-glass opacities	Breast cancer
Oxaliplatin	Cytotoxic	Interstitial opacities	Colon cancer
Everolimus and temsirolimus	mTor	Interstitial opacities	Lung cancer and renal cell
Gefitinib	TKI EGFR	Interstitial pneumonitis, diffuse alveolar damage, fibrosis, and alveolar hemorrhage	Lung cancer
Erlotinib	TKI HER1/ EGFR	Severe pneumonitis and respiratory failure	Lung cancer
Imatinib	TKI	Pneumonitis	GIST and CML
Sorafenib	MKI	Interstitial pneumonitis	HCC and renal cell

CML, chronic myelogenous leukemia; EGFR, endothelial growth factor receptor; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; HER, human epidermal growth factor receptor; MKI, multitargeted kinase inhibitors; mTor, mammalian target of rapamycin; STKI, serine/threonine kinase inhibitor; TKI, tyrosine kinase inhibitor.

radiation. Multiple agents including the cytotoxic therapies and the newer cytotoxic and the targeted therapies can cause pulmonary toxicity.

There are many different patterns of pulmonary toxicity, including hypersensitivity pneumonitis, nonspecific interstitial pneumonitis, cryptogenic organizing pneumonia (bronchiolitis obliterans organizing pneumonia), and diffuse alveolar damage. A sample list of agents that cause pulmonary toxicity is listed in the Table.[1-4]

Computed tomography (CT) findings include ground-glass nodules and opacities, reticular nodules, interstitial opacities, and consolidative opacities. Findings vary among the causative agents (Figs. 1-3). Correlation with the type of chemotherapy and timing of chemotherapy is crucial. Drug toxicity is a potential imaging pitfall, as the varied imaging presentations can mimic pneumonia and metastatic disease. Treatment is with cessation of the agent and corticosteroids.[5]

Pulmonary Hemorrhage

Although diffuse alveolar hemorrhage has been reported with hematological malignancies treated with chemotherapy and stem cell transplantation, severe pulmonary hemorrhage (PH) has now been reported as a toxicity of some of the targeted therapy agents. Bevacizumab has been associated with fatal PH; the risk factors include squamous histology, baseline tumor cavitation, and vessel infiltration.[6,7] Drugs such as sorafenib and sunitinib have also been reported to cause PH.[3,8] Drugs such as rituximab, used in treatment of lymphoma, and gefitinib are also associated with PH. On CT, there are bilateral ground-glass opacities that represent alveolar filling with blood. "Crazy paving" may be present.[9,10]

Pleural Complications

Pleural Effusion

Chemotherapy agents can cause fluid retention because of their mechanism of action. If a patient has interval development of significant pleural effusion, it may be because of

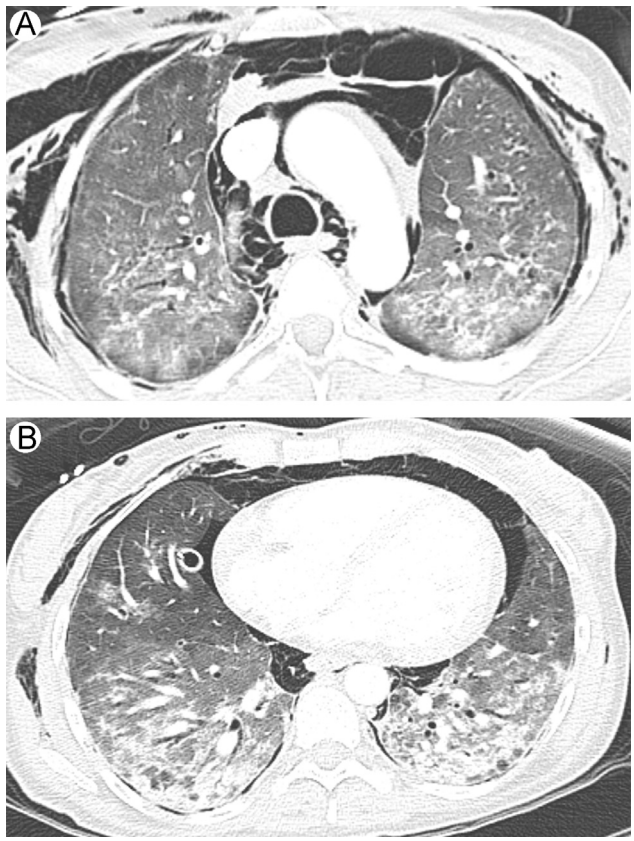

Figure 1 Pulmonary toxicity due to chemotherapy—bleomycin. A 33-year-old woman with Hodgkin's lymphoma treated with Adriamycin, bleomycin, vinblastine, dacarbazine, and rituximab for 7 months. The patient developed progressive pulmonary opacities throughout both the lungs, compatible with drug toxicity due to bleomycin. Despite discontinuation of bleomycin, she developed pneumothoraces, pneumomediastinum, and subcutaneous emphysema because of the lung disease. (A and B) Axial CT images in lung windows show diffuse ground-glass opacities throughout both the lungs and air in the pleural space, mediastinum, and subcutaneous tissues. As her bleomycin-related drug toxicity was steroid refractive, she required care in the intensive care unit and ventilatory support.