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Short Communication

Reactivation of pulmonary tuberculosis during cancer treatment

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ABSTRACT

Reactivation of *Mycobacterium tuberculosis* can occur in patients with latent tuberculosis (TB) with risk factors including chronic disease (i.e., malignancy). We herein describe the case of an immigrant from Hong Kong with lung cancer and no known TB disease who presents with reactivation of TB in the setting of chemotherapy and radiation therapy.

Clinical practice points

- Tuberculosis (TB) reactivation occurs in immunosuppressed individuals.
- Both the Centers for Disease Control and Prevention and American Thoracic Society recognize that cancer is a risk factor for developing TB.
- Doublet platinum-based chemotherapy is the mainstay of treatment for nonsmall cell lung cancer.
- Radiation therapy affects both healthy, viable tissue and malignant cells.
- Combined chemotherapy and radiation therapy can elevate the risk for developing infections.

Case report

A 61-year-old Cantonese-speaking man from Hong Kong presented with a productive cough and fever of 3 weeks duration. He had a history of Stage IIIA squamous-cell carcinoma of the right lung with mediastinal lymph node involvement that was diagnosed 6 months prior to this admission. He

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completed three cycles of neoadjuvant chemotherapy with cisplatin and gemcitabine 2 months prior to admission. Follow-up chest computed tomography (CT) imaging showed extensive air-space consolidation that was contiguous with an obstructing right upper lobe tumor. A restaging positron emission tomography-CT showed a right upper lobe tumor measuring $2.2 \times 2.2\ cm^2$ and a concomitant consolidation in that lobe. He was evaluated by thoracic surgery for a possible surgical resection; however, the therapeutic benefit was low given the extent of his disease. Therefore, his treatment regimen was changed to three cycles of docetaxel and carboplatin with concomitant radiation therapy at a dose of 5940 cGy over 33 fractions to the right lung, which he completed 7 weeks prior to admission. His Karnofsky performance score was 80 throughout his course with an Eastern Cooperative Oncology Group performance status of 1.

On this presentation, he was evaluated by his primary care physician who noted a new leukocytosis and a cavitation at the site of his cancer with communication to the right upper lobe bronchus on CT imaging (Fig. 1). The patient was started on broad-spectrum intravenous antibiotics for the possibility of a bacterial pneumonia with abscess formation; however, his symptoms did not resolve. Acid-fast bacilli (AFB) staining results were positive. He was started on rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE therapy) as an outpatient. His AFB culture eventually returned positive for *Mycobacterium tuberculosis* and a DNA probe completed by the Department of Health confirmed this diagnosis. He was admitted to the hospital after continued cough, which was now associated with weight loss. In addition, he has an 8-month-old grandchild in the home and had no ability to self-isolate. He was continued on RIPE therapy.

During the course of his hospitalization, sputum AFB samples were sent daily to the laboratory until a negative result was obtained. After 30 days, he was eventually discharged home to continue on isoniazid, rifampin, and pyrazinamide. In the setting of active tuberculosis (TB) and concomitant lung cancer, he was started on a less-aggressive chemotherapy regimen with weekly vinorelbine; however, despite this his cancer has progressed. He is currently being considered for a clinical trial.

Written informed consent was obtained from the patient (available upon request).

Discussion

TB management has changed very little in the past four decades. In the United States, screening for latent TB has been a crucial part in the control of TB. Both the Centers for Disease Control and Prevention (CDC) and the American Thoracic Society (ATS) have recognized for over four decades that cancer is a recognizable risk factor for the development of TB [1]. The 2000 ATS guidelines for targeted tuberculin testing and latent TB treatment list the following as oncologic risk factors for the development of active TB: leukemia, lymphoma, and carcinomas of the head and neck [1]. The purported mechanism of action suggests a reduction in local infection barriers at the site of cancer and/or increased susceptibility due to immunosuppression, thereby leading to the inability to fight infection [2]. Although it is recognized that hematologic malignancies increase the risk of developing active TB, the link between solid-organ malignancies and developing TB is less known. A case series of patients with cancer at a tertiary hospital in South Korea showed that those patients with solid-organ malignancy had a 4.7 times greater risk of developing active TB compared with those patients without malignancy [3,4]. A case series in multiple hospitals in Japan in 1990 involving 445 cases showed that various types of solid-organ malignancies placed patients at risk for active TB and that the introduction of chemotherapeutic agents increased the risk of TB progression [5]. Over a 10-year span at the MD Anderson Cancer Center, only 30 cases of active TB were identified in non-human immunodeficiency virus-infected patients, with most found in patients born outside of the United States [6]. Of those 30 patients, the ones receiving higher doses of chronic corticosteroid therapy fared worse and had a greater mortality than those receiving intermittent, cyclic systemic chemotherapy. By contrast, a case series at Memorial Sloan-Kettering in New York City revealed no association between active TB and solid-organ malignancy [7]. At this point, the patient-level response of active (or latent) TB to antitubercular combination treatment is not well described in

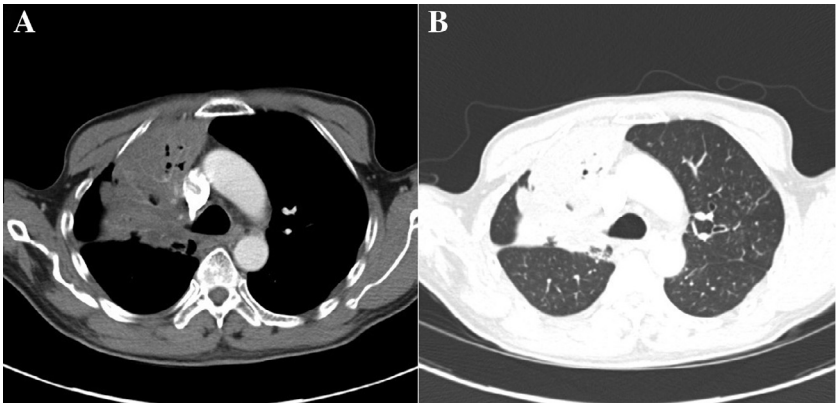

Fig. 1 – (A) Axial contrast-enhanced computed tomography (CT) demonstrates obliteration of the right upper lobe with 'drowned lung' due to atelectasis and bronchial tumor obstruction of the bronchus, mediastinal window, and (B) lung window.

those undergoing cytotoxic chemotherapy other than those described in case series.

Two-drug platinum-based chemotherapy is the standard of care for nonsmall cell lung carcinoma, which has shown a survival benefit in multiple clinical trials in addition to best supportive care [8–14]. Our patient was initially started on combination cytotoxic chemotherapy with cisplatin and gemcitabine, and subsequently transitioned to second-line therapy with carboplatin and docetaxel. Cisplatin and carboplatin are platinum chemotherapeutic agents that work by inhibiting DNA synthesis by interrupting the crosslinking of the DNA helix [15]. Docetaxel works by inhibiting the depolymerization of tubulin thereby inhibiting DNA, RNA, and protein synthesis [16]. The ionizing effect of radiation therapy works by directly damaging the DNA of cancer cells (and normal cells). Our patient had no symptoms of active TB between the first- and second-line doublet chemotherapy regimens. Platinum-based chemotherapeutic agents have radiosensitizing effects that provide better tumoricidal effects when used concomitantly [17–19]. Although no cases of active TB caused by platinum chemotherapeutic agents, gemcitabine, or docetaxel have been reported, there have been cases of reactivation TB reported in patients undergoing radiation therapy [20]. In our patient, we theorize that he most likely had previous latent TB, especially given his higher risk of acquiring TB (i.e., TB-endemic country of origin). There was also an additive effect whereby the systemic toxicity of the chemotherapy in combination with the "spatial deposition of radioactive energy" to both malignant and normal cells led to cancer cell death, the clinical benefit we strive for in treating any malignancy [21]. However, the absence of selectivity of the combined effects does have drawbacks, affecting both healthy, viable tissue and malignant cells, which can affect chemotherapy drug delivery [21]. The effect of radiation on the immune system is thought to involve multiple factors: (a) local tissue damage, which inhibits the body's reaction to infection; (b) peripheral depletion of lymphocytes, thus blunting the systemic immune response; and (c) an alteration in the immune cellular balance, namely, B cells, T cells, and natural killer cells [22–24]. The combination of immune-suppressing chemotherapy in the setting of radiation therapy elevates the risk of primary infections and reactivation of chronic and indolent infections in this patient population.

Conclusion

Little is known about the link between solid-organ malignancy and TB. Reported case series from large academic cancer centers have had conflicting results in patients with solid-organ malignancies. Our patient had squamous-cell carcinoma of the lung and was started on first-line doublet platinum-based chemotherapy before transitioning to second-line chemotherapy with concurrent radiation therapy. He subsequently developed active TB. Given the likelihood of underlying latent TB in this patient prior to the initiation of cancer therapy, he developed active TB likely due to both local tissue and systemic immune factors, thus allowing for this indolent, inactive infection to avoid the natural checks and balances to keep it under control. This case highlights the lack of widely acceptable and established standards for both screening for latent TB and treatment of active TB in patients undergoing treatment for active solid-organ malignancy. We strongly recommend screening all patients born in countries with endemic TB with either a tuberculin skin test (also known as a "purified protein derivative test") or with an interferon-gamma release assay from whole blood to rule out latent TB before beginning radiotherapy or chemotherapy for solid-tumor malignancy. With proper and standardized screening efforts prior to beginning treatment for malignancy, reactivation of TB could effectively be eliminated. Further research is needed to help guide the oncology and pulmonology fields in the management of this special patient population.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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