
CASE REPORT

Pneumocystis jiroveci Infection and Craniospinal Irradiation with Arc Therapy: a Report of Two Cases

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ABSTRACT

Tomotherapy, a form of arc therapy, is often preferred to craniospinal irradiation (CSI) because of its better dose homogeneity when planning target volume and minimising organ risk. We report the cases of two young men with central nervous system germ cell tumour who had unnoticed severe and prolonged lymphopenia after completing CSI with tomotherapy. Both developed Pneumocystis jiroveci pneumonia and one died of respiratory failure. We hypothesise that the rapid drop in lymphocyte count may have been in part due to the 'low dose bath' of radiation to the whole pulmonary vasculature with consequent killing of the circulating lymphocytes, in addition to low-dose radiation to a high volume of the thymus, thoracic duct, and bone marrow. We therefore suggest close monitoring of lymphocyte count during tomotherapy-CSI and consideration of co-trimoxazole prophylaxis in severe lymphopenic patients. Further large-scale study is required to understand the possible correlation of V1-V5 lung dosimetry with risk of lymphopenia.

Key Words: Craniospinal irradiation; Lymphopenia; Pneumocystis jiroveci; Radiotherapy, intensity-modulated

中文摘要

肺囊蟲感染及採用圓弧式照射的脊髓放療：兩例病例報告

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螺旋斷層放療是一種弧形放射治療，由於在規劃靶體積時能達至放射劑量均一性，所以能減少對於其他器官的風險，因而比顱脊髓放療（CSI）較佳。本文報告兩名中樞神經系統生殖細胞腫瘤的年輕患者在接受螺旋斷層CSI後出現了嚴重和持久的淋巴細胞減少症，並未被重視。兩人均有肺囊蟲肺炎，其中一人因呼吸衰竭導致死亡。我們認為導致淋巴細胞數量迅速下降的原因是除了以低劑量輻射照射大範圍的胸腺、胸導管和骨髓外，亦因使用低劑量輻射照射全肺血管而殺死循環淋巴細胞。我們建議使用螺旋斷層CSI時要密切監測病人的淋巴細胞數量，並對於淋巴細胞減少症患者考慮處方預防性藥物co-trimoxazole。須進一步進行大規模的研究以探討V1-V5肺劑量與淋巴細胞減少症可能存在的關係。

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INTRODUCTION

Tomotherapy, a type of arc therapy, is often adopted in children and adolescent cancer patients because of its better dose distribution in terms of sparing organs at risk (OARs) and planning target volume dose conformity. This is particularly relevant for craniospinal irradiation (CSI) in which an extensive planning target volume is required. Tomotherapy is considered better than conformal 3D radiation or intensity-modulated radiotherapy (IMRT) because the 'low dose bath' is often considered less important than dose sparing of particular OARs.¹ CSI is indicated in various types of cancer including central nervous system (CNS) germ cell tumours, a not-unusual type of cancer in Hong Kong Chinese children and young adults.

The effect of radiation on immunity has been studied for a long time. In 1972, Stjernswärd et al² reported that irradiation in breast cancer patients caused a significant drop in T lymphocytes when compared with a control group. Most irradiated breast cancer patients had lymphopenia for at least a year. This observation was also noted in a study reported by Campbell et al in 1973.³ They studied a group of paediatric patients with acute lymphoblastic leukaemia (ALL) and found that although both chemotherapy and radiation caused lymphopenia, the lymphopenia was much more marked in those who had received CSI as prophylaxis against CNS relapse. The difference was still apparent after 1 year. The authors demonstrated that the lymphopenia was largely due to a deficiency of T cells. They hypothesised that T cell deficiency was caused by radiation to the thymus. Both studies confirmed the traditional radiobiology observation that peripheral lymphocytes are extremely radiosensitive despite mitotic inactivity.⁴ Campbell et al³ also found that those ALL patients who received CSI were more likely to die of infection later on.

Although these observations were made over four decades ago, Tang et al⁵ also reported the relationship between lung V5 and lymphopenia in lung cancer patients in 2014, which will be detailed in Discussion.

Pneumocystis jiroveci (previously known as *Pneumocystis carinii*) is an opportunistic fungal pathogen that can cause potentially fatal pneumonia.⁶ It is most often found in human immunodeficiency virus (HIV) infection and is a typical AIDS-defining disease. This is because CD4 T lymphocytes, which are a target of the HIV virus, play a major role in protection against

P. jiroveci. Other patients at high risk of contracting *P. jiroveci* include those with prolonged use of prednisolone, certain rheumatology patients, transplant patients, and certain cancer patients. It is perhaps well-known in the field of oncology that patients prescribed fludarabine or T-cell depleting agent, and glioblastoma patients prescribed temozolomide with concurrent radiation require *P. jiroveci* prophylaxis.⁶

CSI with tomotherapy, nonetheless, is currently not considered a treatment that requires accompanying *P. jiroveci* prophylaxis.⁶ We report the clinical course of these patients with CNS germ cell tumour to illustrate this potential fatal side-effect of CSI.

CASE REPORTS

Case 1

A 21-year-old Chinese man with good past health had a biopsy-proven left basal ganglion non-germinomatous germ cell tumour. He received four cycles of BEP (bleomycin, etoposide, cisplatin) chemotherapy with granulocyte-colony stimulating factor support. Tumour markers alpha fetoprotein, human chorionic gonadotropin, and lactate dehydrogenase showed good response. He was then referred for tomotherapy CSI at another hospital. His radiotherapy (RT) plan was divided into two phases — phase 1 was CSI to 36 Gy (1.8 Gy/fraction); phase 2 was a further 5 fractions of total 9 Gy (1.8 Gy/fraction) as tumour bed boost. His lymphocyte count was $1.2 \times 10^9/l$ (range, $1.0\text{--}3.1 \times 10^9/l$) immediately prior to RT. On day 6 of RT, his lymphocyte count dropped to $0.4 \times 10^9/l$ and dropped further to $0.2 \times 10^9/l$ on day 12. The lymphocyte count fluctuated between $0.1\text{--}0.5 \times 10^9/l$ over the whole RT course. Other cell counts including those of platelets and neutrophils remained normal. Haemoglobin level increased during RT as the patient was recovering from previous BEP chemotherapy.

He was admitted with shortness of breath and high fever up to 39°C 19 days following completion of CSI. He had no previous history of respiratory disease. He required 2 litres of oxygen to maintain his SpO₂ >95%. Chest X-ray showed bilateral lung field infiltrates. Computed tomographic (CT) thorax revealed extensive ill-defined patchy ground glass opacities in both lungs. He was prescribed intravenous augmentin and doxycycline without any improvement. Subsequent bronchoscopy and microscopy of bronchoalveolar washings revealed *P. jiroveci* cysts. Oral co-trimoxazole was commenced for a total of 21 days and fever

subsided after 2 days. He was weaned off oxygen, chest X-ray was clear on day 7, and he was discharged.

His HIV serology was negative. His lymphocyte count was $0.9 \times 10^9/l$ (range, $1.06-3.61 \times 10^9/l$) at follow-up approximately 1 month after the last fraction of RT. He is currently well and being regularly followed up.

Case 2

This was a 26-year-old Chinese man with good past health. He was diagnosed with a pineal gland germinoma (biopsy-proven) with C2 epidural plaque on magnetic resonance imaging (MRI) suggestive of spinal metastasis. Because of developing hydrocephalus, endoscopic third ventriculostomy was performed by neurosurgeons. He was then given 6 cycles of BEP because of spinal metastasis at presentation and an incomplete response on MRI after the 4th cycle. He was referred to another hospital for tomotherapy CSI. The dosage of RT plan was the same as that for patient 1. He had a mild degree of pancytopenia after chemotherapy but was clinically asymptomatic and his pre-RT lymphocyte count was $0.57 \times 10^9/l$ (range, $1.0-3.1 \times 10^9/l$). On day 5 of the CSI, his lymphocyte count dropped to $0.2 \times 10^9/l$. It further decreased to $0.1 \times 10^9/l$ on day 8. His lymphocyte fluctuated between $0.06-0.2 \times 10^9/l$ during the whole course of RT.

He developed an intermittent fever and thrombocytopenia of around $40 \times 10^9/l$ (range, $154-371 \times 10^9/l$) during the latter half of RT. He started developing progressive shortness of breath and high fever 10 days after completion of RT. Chest X-ray at that time showed bilateral lung infiltrates and CT thorax showed ground glass opacities almost throughout the lungs. He was reviewed by a respiratory physician and microbiologist who both agreed a clinical diagnosis of *P. jiroveci* pneumonia (PCP) infection. Polymerase chain reaction (PCR) of PCP DNA was positive on his nasopharyngeal sample.

He ran a rapid downhill course. Although he was prescribed multiple intravenous antibiotics including co-trimoxazole, he gradually desaturated and required intubation and 80% of FiO_2 . He was noted to have a right-sided tension pneumothorax and bilateral surgical emphysema soon after intubation. He was then admitted to the intensive care unit (ICU) and a chest drain was inserted. His disease was uncontrolled and he succumbed on the sixth day of ICU stay. His last lymphocyte count was around $0.11 \times 10^9/l$ (range, $1.06-$

$3.61 \times 10^9/l$). HIV serology was not tested but other microbiological workup was negative.

DISCUSSION

Both patients received a standard BEP regimen (etoposide 100 mg/m^2 on day 1-5, cisplatin 20 mg/m^2 on day 1-5, bleomycin 30 mg on day 2, 6, 16 on 3-week cycle) before proceeding to CSI with tomotherapy. Patient 1 received 4 cycles of BEP for left basal ganglion non-germinomatous germ cell tumour. Patient 2 received 6 cycles of BEP in total for pineal germinoma with suspected drop metastasis. Both had a relatively preserved lymphocyte count during and at the end of chemotherapy. Although BEP is a myelosuppressive regimen, no component of the regimen is believed to have a particularly strong lympholytic effect.

Nonetheless, the lymphocyte count dropped sharply in both patients after commencement of CSI RT. Both patients were treated by tomotherapy with two phases — phase 1 comprised CSI in 36 Gy (1.8 Gy/fraction); phase 2 comprised a further 5 fractions of total 9 Gy (1.8 Gy/fraction) as tumour bed boost. In patient 2, the boost volume was more extensive as there was suspected cervical and lumbosacral spinal metastasis.

Patient 1 had isolated lymphopenia after the beginning of CSI and only recovered almost 2 months after completion of CSI. Patient 2 had extensive pancytopenia in addition to lymphopenia; this may be explained by more cycles of BEP received together with higher volume of tumour boost in phase 2 RT. The well-recognised effect of marrow suppression due to extensive radiation of bone marrow tissue contributed to the lymphopenia and pancytopenia in patient 1 and 2, respectively. Bone marrow radiation, however, was unlikely to have been the only cause of lymphopenia since most mature lymphocytes are in the reticuloendothelial system and in circulation.

Both patients had positive microbiological proof of PCP infection. The diagnosis of PCP was confirmed by bronchoalveolar lavage (BAL) sample microscopy in patient 1, and his lung field was cleared after a few days of co-trimoxazole treatment. No BAL sample was obtained in patient 2, mainly because he presented late in the course of infection, already requiring intubation and high flow oxygen up to FiO_2 80%. Bronchoscopy was not possible but PCR of PCP DNA was positive on nasopharyngeal aspirate. The severity of PCP infection of patient 2 may be explained by his relatively lower

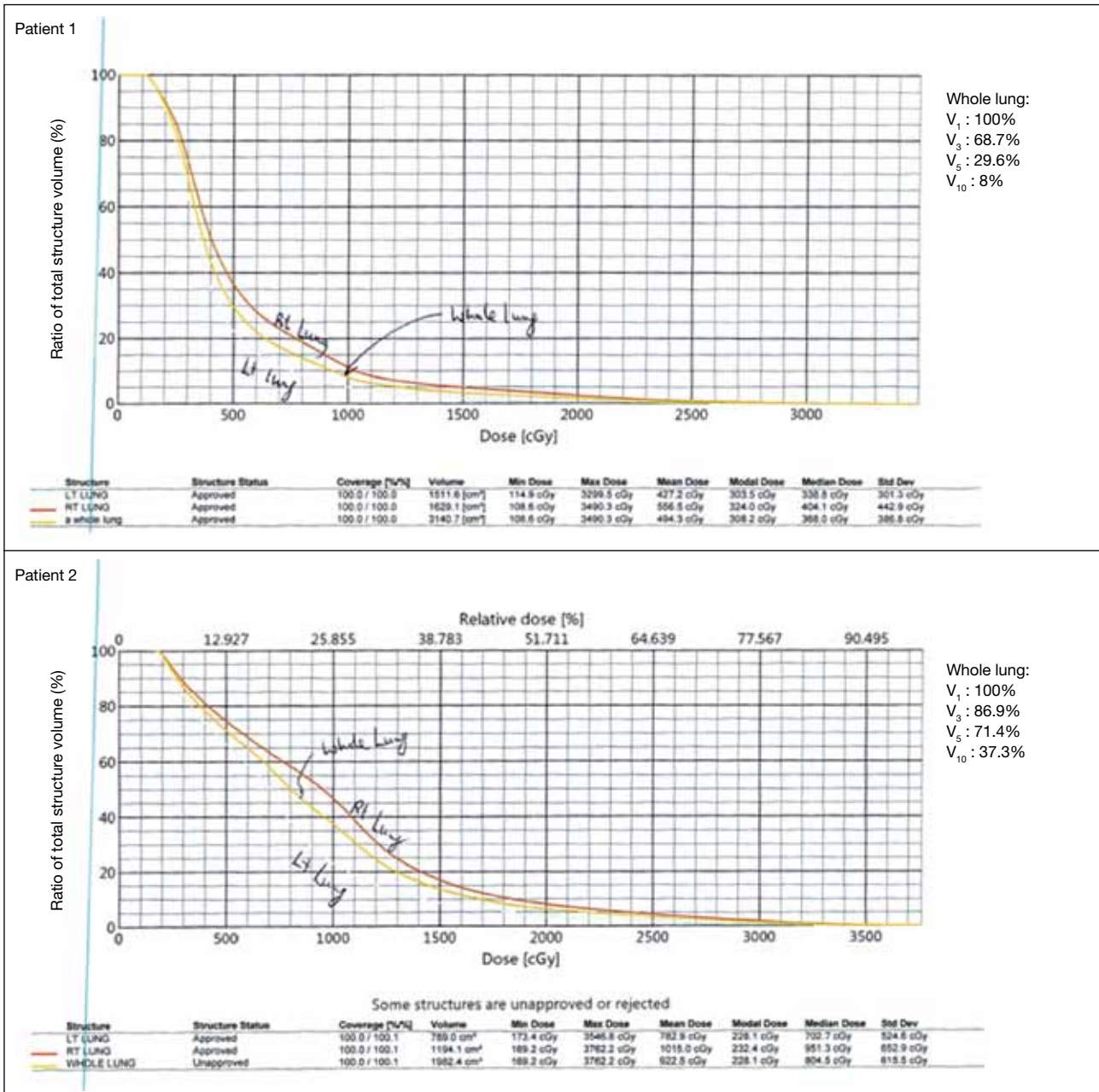


Figure. Cumulative dose-volume histograms of the two patients.

lymphocyte count than patient 1 during RT. Bleomycin-induced pneumonitis may present similarly but should be a diagnosis of exclusion only.⁷

The association of lymphopenia with lung V5 was first suggested by Tang et al⁵ from MD Anderson Cancer Center. Their group studied 711 non-small-cell lung cancer patients who received definitive RT. Analysis of lung dose-volume histogram parameters revealed a markedly significant correlation between lung V5

and lymphocyte nadir ($p < 0.0001$). The Spearman correlation coefficient of combined chemotherapy and radiation group was approximately 0.42 (Figure). This correlation was persistently shown in both groups of patients who received 3D conformal RT and IMRT.⁵ It was suggested by the author that the ‘low dose bath’ of RT killing lymphocytes in lung circulation was the likely explanation.

When compared with IMRT or 3D conformal RT CSI,

tomotherapy-CSI distributes lower doses to larger volumes and higher doses to smaller volumes.⁸ This is often considered an advantage of tomotherapy-CSI to preserve nearby OARs. A potential drawback is that the low dose bath may have an unexpected toxicity on the lungs or gastrointestinal tract, and on total body integral dose.⁸

We hypothesise that since all the cardiac output must go through the whole pulmonary vasculature in each cardiac cycle, most lymphocytes in the circulating blood will be exposed to at least low-dose radiation in the case of tomotherapy CSI in which lung V5 is high. This was evidenced by a recent study by Yovino et al.⁸ They analysed a typical radiation plan for glioblastoma of 60 Gy in 30 fractions, and reported that a single fraction of RT resulted in 0.5 Gy exposure of 5% of circulating cells. Over 30 fractions, 99% of circulating cells would be exposed to at least 0.5 Gy.⁸ As in CSI, the RT field in the lung is much larger than in the glioblastoma RT plan and our patients received 25 fractions in total. It is reasonable to estimate that more than 99% of circulating lymphocytes were exposed to at least 0.5 Gy. Mature circulating lymphocytes are extremely radiosensitive and they exhibit significant DNA fragmentation and fatality even at a low radiation dose (<1 Gy).⁵ It is thus reasonable to hypothesise that larger RT fields affecting the lung would cause more lymphocyte damage.⁵

According to the dosimetry data, both patients' V1 lung values were 100%, meaning that all lung tissue including the pulmonary vessels received 1 Gy of radiation during the course of RT. This confirmed our hypothesis of high 'low dose bath' effect on lung in tomotherapy-CSI. The V3 and V5 values were lower in patient 1 than in patient 2 (Table). This may explain the severity of lymphopenia and grave outcome in patient 2.

In addition, mediastinal radiation is reported to be an independent risk factor for development of PCP in cancer patients.⁹ Barbounis et al¹⁰ suggested that it may be due to radiation to the thoracic duct in the posterior mediastinum, thus decreasing the number of blood

lymphocytes. This hypothesis was also suggested much earlier on by Campbell et al in 1973.³

It is reasonable to postulate that additional factors contributed to the development of PCP infection in our patients. Possible reasons include prolonged myelosuppression from BEP chemotherapy regimen and extensive bone marrow irradiation in CSI. These may also explain why PCP infection is uncommon in lung and breast cancer patients who undergo thoracic irradiation. Whether the 'low dose bath' effect on the lung parenchyma would predispose it to PCP colonisation and infection is uncertain. Given the many benefits of arc therapy (including tomotherapy) in CSI, it would be wise to monitor lymphocyte nadir during and shortly after arc therapy.

Suggestions

National Comprehensive Cancer Network's (NCCN) guideline⁹ suggests that patients at high risk of PCP infection shall receive prophylaxis. These patients include allogeneic stem cell recipients, ALL patients, patients on alemtuzumab, (Cat 1) recipients of purine analog therapy and other T-cell depleting agents, recipients of prolonged corticosteroids or receiving temozolomide + RT and autologous stem cell recipients (Cat 2B). Current prophylaxis options include co-trimoxazole 1 double-strength tablet daily (SMX 800 mg/TMP 160 mg) ; or dapsone 100 mg daily; or atovaquone 1500 mg daily or pentamidine 300 mg monthly aerosolised.⁷

Patients on arc therapy in CSI are not currently considered susceptible to PCP infection. The NCCN guideline suggests that PCP prophylaxis for patients receiving temozolomide and RT "should be continued until recovery from lymphocytopenia".⁹ We believe patients who are on tomotherapy-CSI should also be prescribed prophylaxis. We suggest that larger-scale correlation study of V1-V5 lung dosimetry with risk of lymphopenia should be performed, to clarify the risk of this potential fatal complication of arc therapy in CSI.

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Table. Comparison of cumulative dose-volume histograms between two patients.

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1	100%	68.7%	29.6%
2	100%	86.9%	71.4%

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