Infectious pulmonary tuberculosis in a New Zealand cancer centre

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ABSTRACT

This report details the investigation of oncology and haematology patients, as well as cancer centre staff, friends and family who were exposed to an oncology patient with reactivated pulmonary tuberculosis (TB) in a New Zealand cancer centre. A total of 46 patients, seven staff members and 14 family and friends were identified as being exposed to the index case of TB (Mr K). These people were screened for TB infection by the use of a symptom questionnaire, Qiagen QuantiFeron (QFT)® Gold Plus test and, if potentially immunocompromised, a chest x-ray (CXR). There were no confirmed secondary cases of TB in any of the groups screened for infection, but surveillance for signs and symptoms of TB disease in those with significant risk is ongoing. In this article we discuss the public health response to TB in a cancer centre and potential preventative strategies for the future.

Mr K is a 67 year old Māori male who was a heavy smoker and presented with substantial weight loss (15kg in six months), central abdominal pain and melaena for two weeks. He had no significant past medical history or known TB contact. He was diagnosed with gastric cancer on gastroscopy. A staging positron emission tomography-computed tomography (PET-CT) scan showed the cancer was confined to the stomach without any lymph node involvement. The PET-CT scan also demonstrated some non-specific inflammatory changes in the left lung upper lobe, which were thought to be due to a concurrent chest infection at the time of the PET-CT. A staging laparoscopy confirmed no spread of the cancer outside the stomach. He commenced neoadjuvant FLOT (5-Fluorouracil, Folinic acid, Oxaliplatin, Docetaxel) chemotherapy, administered fortnightly at the hospital's cancer centre, with the aim of curative intent following a gastrectomy.

He tolerated the first cycle of chemotherapy well. However, the second cycle of chemotherapy was delayed due to worsening of his chronic 'smoker's cough'. This cough partially improved without further investigation or intervention. He received two further cycles of chemotherapy. A repeat PET-CT scan to assess treatment response revealed reduction in the size of the gastric cancer but worsening parenchymal change and new cavitating lesions in the left upper lobe, suggestive of pulmonary TB. He underwent an urgent bronchoscopy. Spontaneously produced sputum and bronchial washings were both strongly positive for acid fast bacilli on Ziehl–Neelsen stain, and cultures grew *Mycobacterium tuberculosis* within four days. He was commenced on anti-TB therapy while awaiting sensitivities. Sensitivities later showed the organism to be fully sensitive to first-line agents. He went on to have an uneventful and successful treatment of his pulmonary TB. His gastric cancer initially responded to the chemotherapy and surgery, with no evidence of disease recurrence a year after his surgery. However, in May 2019 he presented again to hospital with abdominal pain. A repeat CT abdomen demonstrated recurrence of his gastric cancer with intraabdominal metastatic disease. Mr K sadly died from metastatic gastric cancer in June 2019.

Public health investigation

The risk of healthcare-associated infection and the vulnerability of the exposed patient population was immediately recognised. The Medical Officer of Health was notified and an interdepartmental response group was formed to manage the incident.

The aim of the response was to minimise the risk of further exposure to TB, and also identify, screen and test for TB infection in anyone with significant contact. Contacts were also provided with information and advice about the symptoms of TB, and what to do should they experience these symptoms.

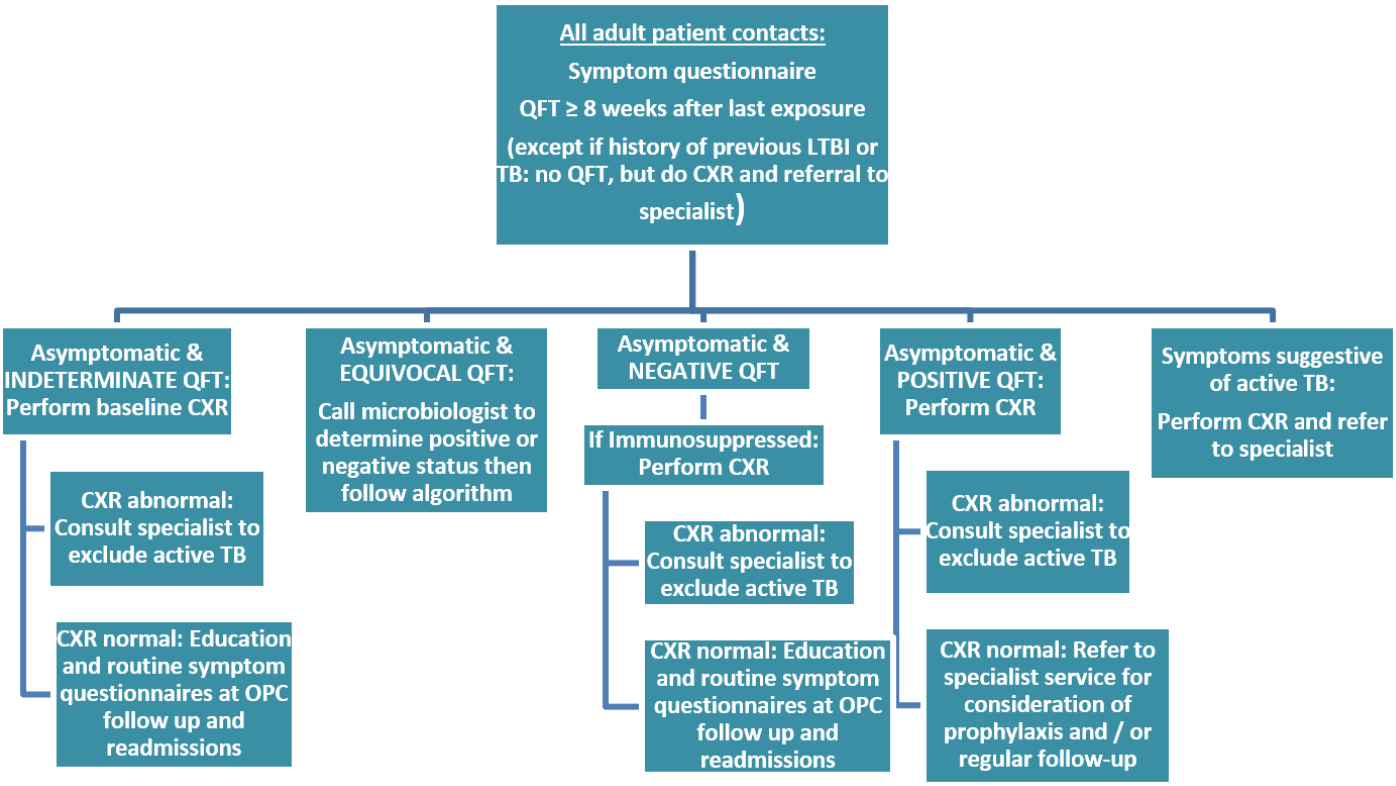
The cancer centre is an open ward with dimensions of 21 metres long by 5 metres wide and 2.4 metres high. It has 10 armchairs and one bed for patients, which encircle the perimeter of the room. Each armchair is separated by approximately two metres. Patients sit in these armchairs while receiving chemotherapy. There are curtains surrounding one of the armchairs and the bed, but these are seldom used.

Patient and staff records were sourced to establish the estimated duration of exposure to Mr K by staff and patients. An algorithm used in a previous similar incident (see Figure 1 for testing algorithm) was used to decide who warranted testing for TB. The contact tracing of friends and family was commenced immediately.

The following definition of a 'contact' was created based on the *Guidelines for Tuberculosis Control in New Zealand 2010*.[1] The time period for identifying potential contacts was set at three months prior to Mr K's diagnosis of TB, as recommended by the guidelines when the date of cough onset is not known (as was the case). In order to clarify those at elevated risk of acquiring TB we used the following contact definition:

"A person with greater than eight hours of cumulative exposure to the case, in a closed environment during the three months prior to the case's Tuberculosis diagnosis OR an immunocompromised person with more than three hours of cumulative exposure to the case, in a closed environment, during the three months prior to the case's Tuberculosis diagnosis."*

Figure 1: Tuberculosis exposure screening and testing algorithm.[2]



(*A single dose of chemotherapy or a blood transfusion was estimated to take an average of 3 hours; therefore any patient who had received chemotherapy or blood products on the same day as the index case was considered to be at risk and qualified for screening.)

All family and friends (immunocompetent) of Mr K with significant exposure were identified and screened with an immediate and an eight-week post-exposure QFT test if they met the contact definition. Some contacts lived outside the local public health unit's catchment area, therefore other public health units assisted with contact tracing.

Staff members (immunocompetent) who met the contact definition were screened with a symptom questionnaire and an eight-week post exposure QFT test.

All oncology and haematology patients undergoing treatment at the cancer centre were assumed to be immunocompromised. An algorithm (Figure 1) for appropriate investigation of these contacts was adapted from another district health board, who had responded to a similar incident among immunocompromised patients exposed to TB.[2] Given the lower sensitivity of QFT in immunosuppressed hosts,[3] exposed patients were screened using both QFT test and a CXR.

All patients who met the contact tracing threshold were phoned by a clinician to discuss the situation and provide an opportunity for questions. A letter outlining the situation and management was also sent to patients and their general practitioner (GP) and oncologist or haematologist. All patients were phoned with results as these became available, with explanation of the test results and any further action required. A final summary letter containing individual contacts' test results and public health recommendations was sent to all patient contacts, their GPs and their oncologist or haematologist, with advice to remain vigilant for TB signs and symptoms for at least two years.

All staff who met the exposure threshold were identified and informed of the situation and testing requirements by the occupational health and safety department. The test results were reported to each staff member by occupational health and safety.

Results

Family

Fourteen family and friends of Mr K met the contact definition and were screened by their local public health unit. One adult underwent serial Mantoux® testing by his GP, and the remainder were tested using an immediate and eight-week post-exposure QFT. All family and friends were asymptomatic for symptoms of TB disease and QFT negative.

Staff

There were a total of 15 staff members, identified by occupational health and safety, who had been in contact with Mr K during his infectious period. Only four of these staff members met the contact definition criteria. These staff members were screened with a symptom questionnaire and an eight-week post-exposure QFT test.

A further three staff members, who did not meet the contact definition threshold requested to be tested for reassurance. All seven of the screened staff members were asymptomatic for symptoms of TB disease, and all had negative QFT tests.

Patients

There were 55 patients who were identified as being present in the cancer centre on the same days as Mr K. Of these people, 46 met the contact definition.

Four patients passed away in the period between exposure and screening of contacts. After discussion with their respective oncologists or haematologists, none of these deaths were thought to be caused by TB disease, nor were there any concerns of active TB symptoms prior to their death.

The remaining 42 patients were screened with both a symptom questionnaire, eight-week post exposure QFT test and a CXR. Of these 42 patients, five had symptoms which may have been consistent with TB disease. Of these five patients, four had stable symptoms that either preceded their exposure or their symptoms were thought to be a manifestation of their underlying malignancy. In all four cases the eight-week post-exposure QFT tests were negative, and their CXRs did not have features suggestive of TB. One of the five symptomatic patients had developed a new non-productive cough

since being exposed, however their QFT test was negative and their CXR showed indeterminate right upper lobe focus. Close monitoring for signs suggestive of TB and a repeat CXR in three months was advised after discussion with an infectious diseases specialist. The repeat CXR demonstrated slight enlargement in the indeterminate right upper lobe focus, which was further evaluated using a computed tomography chest scan and reported as a new primary lung cancer.

The 37 asymptomatic patients all had negative eight-week post-exposure QFT tests. One patient had right upper lobe interstitial changes/fibrosis on CXR, and after discussion with an infectious diseases specialist a repeat CXR was advised in three months, with close monitoring for symptoms of TB. The repeat CXR showed an increase in the right upper lobe interstitial changes/fibrosis, which was also further evaluated using a computed tomography chest scan and reported as progressive right upper lobe post-radiotherapy fibrosis. See Figure 1 for the flow chart of the screening and results.

Discussion

Diagnosis and management

The management of malignancies is rapidly changing. Many cancer treatments cause immunosuppression, increasing the risk of opportunistic infections.

Reactivation of latent pulmonary TB or progression of TB disease is a known complication among people receiving chemotherapy.[4] In the case described, the combination of chemotherapy and the marked malnutrition from gastric malignancy most likely led to the reactivation of latent pulmonary TB: there was progression of a chronic cough and worsening appearance of lung disease on repeat PET-CT scanning following the initiation of chemotherapy.

TB is a relatively uncommon disease in New Zealand. There is an incidence of 7–10 cases of TB disease per 100,000 people per year.[1] Notably, TB often presents with signs or symptoms that may be attributed to other diagnoses (including malignancy). Consequently, it is not always at the forefront of a physician's mind. This situation was unusual and unfortunate in terms of both the large number and the susceptibility of the contacts involved. Due to the open plan of the cancer centre and the insidious nature of our case's symptoms, a number of immunosuppressed patients were exposed before the diagnosis of TB was made.

A key to the successful management of this situation was the collaborative approach across departments and the clear lines of communication. Colleagues from Public Health, Infectious Diseases, Infection Prevention and Control, Oncology, Occupational Health and Safety were involved in this response. This group included clinicians, managers and also a communications expert with experience in risk communication. Clear communication was a priority in this challenging situation and involved both internal communications with the response team, and also communication with affected staff, patients and the public if necessary. Regular team meetings, shared files and collated email updates were used to ensure everyone was working with the same information and that relevant stakeholders were kept informed. Furthermore, every patient involved in this incident was phoned by a doctor or TB nurse specialist and sent written information; including the contact details for a clinician should they have questions. This information was also communicated to primary care, and the relevant oncologist or haematologist. Information was also recorded in occupational health records for affected staff.

Investigation of the event

The standard TB symptom screening questionnaire among this patient population was of limited value, as the systemic symptoms of TB are similar to those of malignancy and haematological disorders. Fatigue, fevers, night sweats and weight loss may reflect progression of malignancy rather than development of TB disease. Even respiratory symptoms such as cough, haemoptysis and shortness of breath may be a manifestation of a primary lung cancer or pulmonary metastases as opposed to pulmonary TB. Interpreting symptoms in this patient population was difficult. Therefore the timing of the patient's symptoms and their known exposure date was important to distinguish between the possibility of TB and the patient's known malignancy. A further complicating factor among this patient

population was that the QFT test used for screening of contacts is less sensitive due to the depletion of lymphocyte populations with chemotherapy.[2] Due to this recognised loss of QFT test sensitivity, immunocompromised patients were also screened with a CXR to help improve the reliability of detecting TB. This issue was well illustrated in one immunocompromised contact who had received ablative chemotherapy prior to a bone marrow transplant. Their QFT test result was reported as indeterminate, likely due to a lack of interferon production (T-cell response) from a demonstrable lymphopaenia.

Mr K had many features of high infectivity (smear positive pulmonary disease, cough longer than 10 weeks and cavitating lesions on CXR), yet to date there have been no confirmed secondary cases of TB. However, surveillance of patient contacts by their oncologists, haematologists and GPs is ongoing. A possible reason for this lack of transmission may be Mr K's reserved nature: many of the staff in the cancer centre noted that he tended to "keep to himself". Given that there is no evidence of transmission in any of the identified contacts, the risk of transmission is likely to have been overestimated and a less extensive contact tracing may have been appropriate, however because Mr K did not live in the same household as any of his close contacts, an estimation of his infectivity was not able to be determined, and therefore broad contact tracing was undertaken.

This incident occurred among a group of patients who are often (understandably) already stressed and anxious due to their cancer diagnosis and treatment. The team managing this event was mindful of the potential for psychological harm by both alerting cancer patients to this TB exposure and screening for TB infection. However, it was felt that honest communication and transparency was important in managing this situation, and that patients were entitled to have clear information about their exposure to TB and the potential risks to them. Overall it was believed that the benefits of identifying any TB infected patients outweighed the potential psychological harms to the patient group from anxiety related to the TB exposure and any distress related to false positives identified in the initial screening process. Importantly, in managing this event the patient concern and anxiety was managed by reassuring patients that their total exposure was likely to be small and that early identification of an infection would reduce the risk of harm. Furthermore, each patient was phoned with the results of their TB screening to provide additional reassurance, with the proviso that they remain vigilant for any new symptoms suggestive of TB.

Risk assessment and screening of patients undergoing chemotherapy

This situation raises the question of whether TB risk-assessment and consideration of pre-treatment screening should be performed among oncology patients as part of routine work-up prior to chemotherapy. In other medical specialties where immunosuppressive monoclonal antibodies are used, clinicians routinely screen for TB in all patients prior to commencement of these therapies.[5] However, it is not currently routine practice for cancer patients to undergo TB screening before starting chemotherapy.

A 2017 systematic review from the European Respiratory Journal confirms that chemotherapy patients have an increased risk for developing TB compared to the general population.[6] The authors recommend that given the limited period of immunosuppression in cancer patients and the reduced cumulative lifetime risk of TB disease (due to reduced life expectancy) patients with cancer undergoing chemotherapy do not warrant screening for latent TB infection. However, this recommendation does not extend to children with curable cancers who have a longer life expectancy. The authors of this review advise that adult cancer patients with risk factors for latent TB (family history, previous exposure or birth in a country with high rates of endemic TB) and paediatric cancer patients should be considered for QFT testing before starting chemotherapy. However, detailed guidance on how to quantify risk or what process of screening should be followed does not exist in the published literature.

In 2005–2009 in New Zealand the incidence rate of TB among Māori was five times that of Europeans and 10 times more common among Pacific peoples than in

Europeans. In Asian ethnic groups the rate is 25 times greater than in Europeans, however the TB incidence by ethnic group is confounded by place of birth.[1] It therefore may be sensible to target TB screening for pre-chemotherapy patients towards Māori, Pacific people and Asian ethnic groups, particularly those born outside of New Zealand, who are at higher risk of having TB. This will not only assist in the diagnosis and treatment of TB but also reduce the risk of complications during treatment, increasing the likelihood of improved survival and quality of life.

It is important to recognise that screening for TB has both potential harms and benefits. A systematic approach to TB screening in pre-chemotherapy oncology patients needs to weigh up the potential costs, both financial costs and patient harms (invasive investigation following false positive results, psychological harm of false positives and inappropriate reassurance in the case of false negatives), against the importance of preventing the spread of infection among other patients and the public. Further research is required to develop and validate a screening tool that will assist clinicians to determine the risk of latent TB in a prospective chemotherapy patient and ensure that QFT testing is used appropriately.

Another lesson from this incident is that close attention to cancer centre design and infection control policy may be important to minimise the risk of communicable disease spread among vulnerable patient populations and healthcare staff. Importantly, the investigation of this case did not identify any secondary cases of TB despite the multiple features, high infectiousness in our case, and the prolonged exposure of many immunocompromised patients in a small open-plan cancer centre. Open-plan healthcare facilities are important for social interaction and patient wellbeing, during what is often a stressful and socially isolating time, with frequent and sometimes lengthy treatments in hospital. However, social interaction may come at the cost of an increased risk of the infectious disease spread. The trade-off between these two aspects of patient health is an important discussion, and not one with a clear-cut answer. Going forward, this case also highlights the responsibility of both patients and staff to follow their respective cancer centre's infection control policy when patients present with symptoms that could be from an infectious illness.

Conclusion

Incidents with potentially significant public health consequences, such as the situation described, necessitate the collaboration of a multi-disciplinary team of health professionals to ensure a rapid and coordinated response to identify and minimise risk to the public. Effective communication between all responders involved is crucial to a desired outcome.

Chemotherapy often creates a state of immune compromise, increasing the risk of either acquiring or reactivating infectious diseases, including TB. Reactivation of infectious diseases in chemotherapy patients can have serious negative consequences for both the patient and also family, staff and other immunosuppressed patients.

Current evidence points us to the importance of vigilance for symptoms, infection prevention and control strategies and public health management of TB. However, there is a lack of evidence and protocols for evidence-based decision making on how to risk-assess and manage screening of TB in pre-chemotherapy cancer patients.

Competing interests:
All authors are currently employed by the Bay of Plenty District Health Board.
Acknowledgements:
We would like to thank the patient, Mr K who kindly gave us permission to publish this article before he died, may he rest in peace. We are also grateful to all members of the team who worked collaboratively and professionally to respond to this incident, including our colleagues in Infection Prevention and Control, Occupational Health, Oncology and Haematology, Communications, Infectious Diseases and Toi Te Ora Public Health.
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http://www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2019/vol-132-no-1503-4-october-2019/8007

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