

An Unexpected Infection in A Lung Transplant Patient

February 7, 2024



**WEST COAST
TRANSPLANT ID**

Khuloud Aldhaheri, MD FRCPC

TxID Clinical Fellow

University of British Columbia



THE UNIVERSITY
OF BRITISH COLUMBIA



Case

□ A man [REDACTED] with the following past medical history:

- Anti-synthetase syndrome ([REDACTED] myositis, **interstitial pulmonary fibrosis**, polyarthrititis) status post right single lung transplant in [REDACTED] 2012
- Varicella Zoster Virus Infection (VZV)
 - keratoconjunctivitis – [REDACTED] 2021
 - Disseminated VZV (Skin, esophagus, lung) – [REDACTED] 2018
- Bladder cancer – treated with intravesical immunotherapy and chemotherapy and transurethral resection (TUR) in 2019
- Paroxysmal atrial fibrillation
- Left retinal detachment – s/p surgery in [REDACTED] 2019
- Chronic kidney disease – baseline serum Creatinine (130-150 mmol/L)(1.47 – 1.7 mg/dl)
- Type 2 Diabetes mellitus (HbA1C 7%)

Case

Illness course

2012
Single right lung transplant



- Admission for transplant
 - Single right lung transplant
 - CMV D+/R+
 - EBV D+/R+
 - Maintained on prednisone 5 mg, mycophenolate sodium EC 720 mg BID, tacrolimus (target 6-8 ng/mL)
 - Completed valganciclovir prophylaxis, maintained on TMP-SMX prophylaxis, azithromycin qMWF

- During this admission, hospital contact of a pulmonary tuberculosis case in critical care unit at Vancouver General Hospital (2012)
 - T-spot and follow-up recommended
 - No records of this

Case

Illness course



COVID-19 respiratory tract infection

- Admitted to hospital, on room air.
- Treated with
 1. IV Remdesivir 200 mg once followed by 100 mg daily for 2 days
 2. Methylprednisolone pulse steroid for 3 days and then 60 mg followed by a taper by 5 mg every 3 days until at 5 mg. Then continue 5 mg daily
 3. Intravenous immunoglobulins 0.5 per kg once
 4. Valganciclovir prophylaxis given augmentation of immunosuppression, CMV viral load undetectable at the time

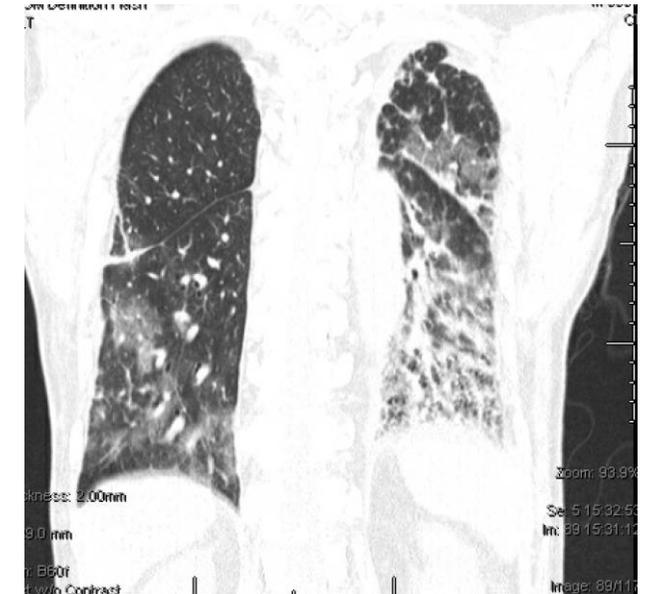
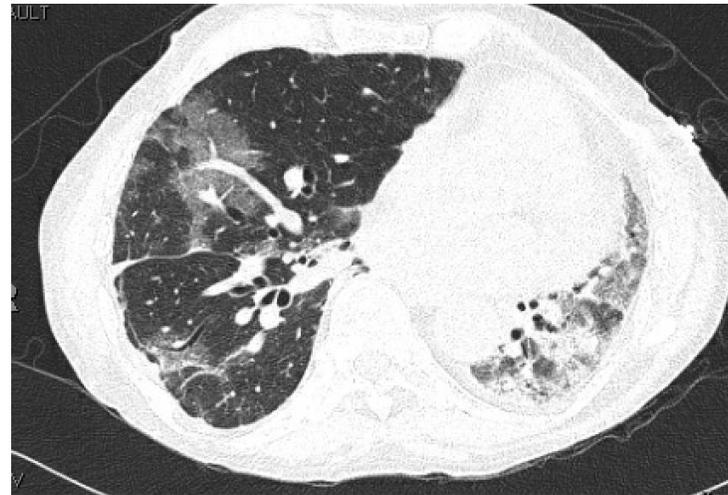
Case

Illness course

2012
Single right lung transplant

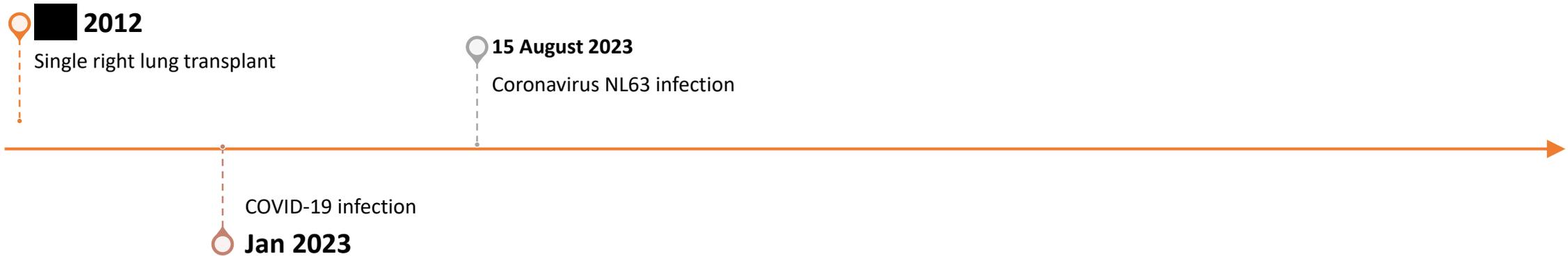
COVID-19 infection
Jan 2023

Test	Results
Leukocyte	6.2 x10 ⁹ /L
Lymphocyte	0.2 x10⁹/L
Neutrophils	5.6 x10 ⁹ /L
Hemoglobin	109 g/L
Platelets	210 x10 ⁹ /L
Creatinine	174 mmol/L (1.97 mg/dl) GFR 34 mL/min
Urinalysis	Negative leukocytes and blood



Case

Illness course

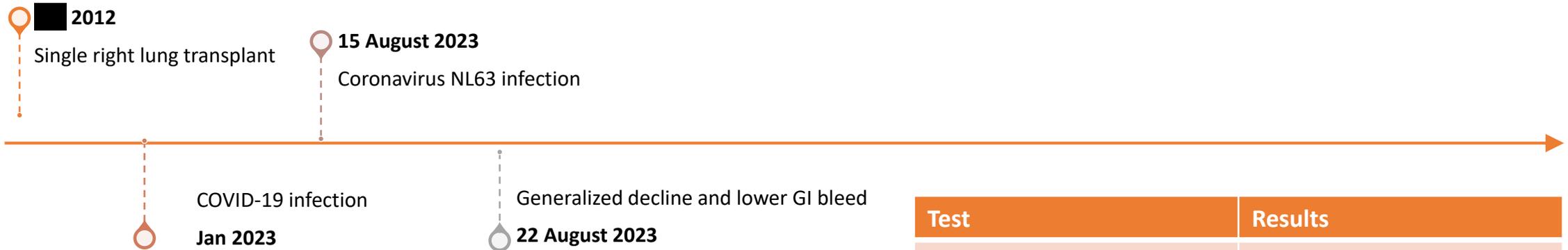


☐ Coronavirus NL63 infection

- Treated in a community hospital
- A mild decline in spirometry was noted
- Treated with methylprednisolone pulse for 3 days
- IVIg x 1 on 18 Aug23
- Follow up spirometry improved

Case

Illness course

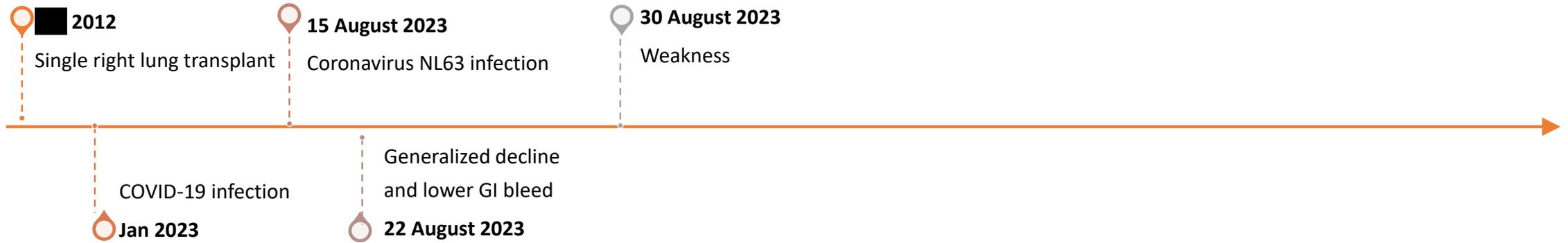


- Generalized decline and lower GI bleed
 - Weakness and further decline
 - Lower GI bleed – Hemorrhoidal
 - 1 unit PRBC
 - Valganciclovir
 - Mycophenolate sodium reduced to 500 mg BID
 - Discharged

Test	Results
Leukocyte	3 x10 ⁹ /L
Lymphocyte	0.2 x10 ⁹ /L
Neutrophils	2.1 x10 ⁹ /L
Hemoglobin	81 g/L
Platelets	96 x10 ⁹ /L
Creatinine	218 mmol/L (2.47 mg/dl) GFR 26 mL/min
CMV serum PCR	234 IU/mL
Urinalysis	Moderate leukocytes

Case

Illness course

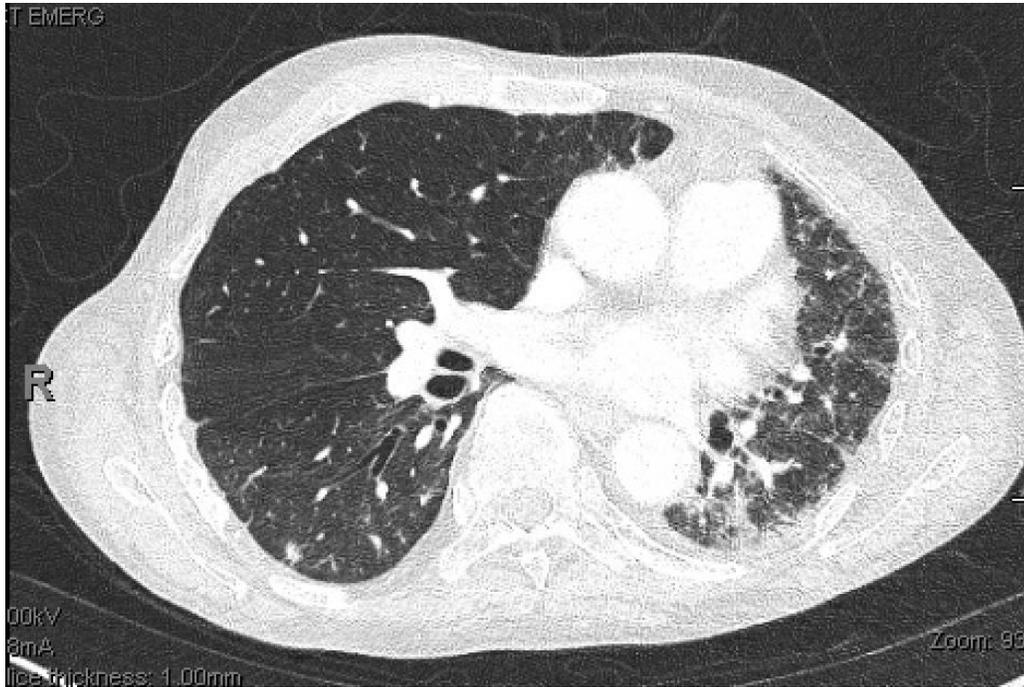


Case

❑ Weakness

- Body aches, shivery all the time, decrease enteral intake, left wrist pain
- Seen by GI for worsening normocytic anemia “Upper endoscopy: mild gastritis”
- Seen by Rheumatology for left wrist pain
 - Crystal induced monoarthritis – elevated uric acid
 - Colchicine, prednisone (50mg x3 days and decrease by 10mg q3d until back to maintenance of 5mg po daily)
- Seen by Hematology for bicytopenia (platelets, hemoglobin) - CKD, MMF, recent CMV
- CT chest/abdomen/pelvis: **New right lower lobe ill-defined centrilobular nodularity** suspicious for low-grade infection/bronchiolitis. Mild **right more than left urothelial thickening** involving the renal pelvis and proximal ureters
- Urinalysis trace leukocytes. Urine culture: E. faecalis with negative repeats x2
 - Treated with 2 weeks of piperacillin-tazobactam
- Mycophenolate sodium EC changed to azathioprine

Case



Case

Illness course



Dysuria

- Dysuria, urinary frequency and urgency, no documented fever but ongoing shivers (duration ~ 3 months)
- CT abdomen/pelvis:
 1. Non-specific **centrilobular nodularity in the graft** (new) and native left lung end stage fibrosis.
 2. **Right anterior bladder wall thickening persists, presumably the known bladder tumor.**
 3. No CT features of pyelonephritis, although this does not exclude the diagnosis.
 4. Progression of right external iliac and suspected perivesicular **adenopathy**.
 5. 2.2 x 2.5 cm left prostate nodule

Question 1

Urology called Transplant Infectious Diseases, concerns for prostatic abscess and prostatitis. Question about empiric antibiotics and work up?

What would be your suggestions in terms of infectious differential diagnosis and further work up?
(Please type as free text)



Case

Illness course

Test	Results
Leukocyte	11.9 x10⁹/L
Lymphocyte	0.1 x10⁹/L
Neutrophils	11.2 x10⁹/L
Hemoglobin	92 g/L
Platelets	173 x10⁹/L
Creatinine	180 mmol/L (2.04 mg/dl) GFR 32 mL/min
CMV serum PCR	<35 IU/mL
Urinalysis	Large leukocytes Trace blood
Urine culture	No growth
Blood culture	No growth
C-reactive protein	90 mg/L
Prostate Specific Antigen	Negative

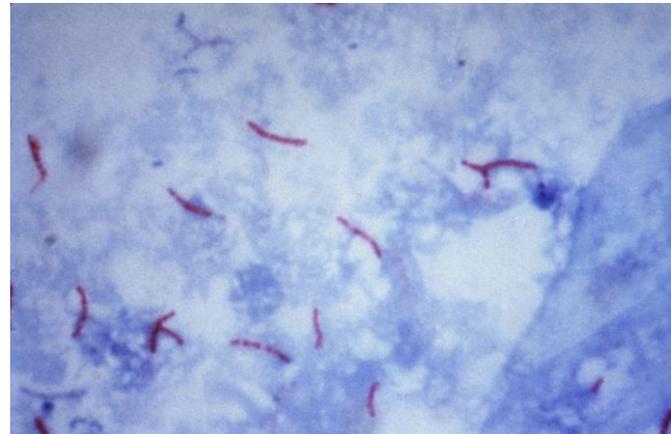
❑ Transplant ID

- CT abdomen/pelvis discussed with Radiology and Urology, prostate nodule felt less likely to be in keeping with prostatic abscess
- Urology deferred aspiration and biopsy this admission (DOAC), suspect this is a benign prostatic hyperplasia nodule
- Transplant ID recommended:
 - Hold antibiotics
 - Urine AFB
 - Urine BK PCR
- Patient discharged

Question 2

□ On 4th October 2023

- Transplant ID gets a call from BCCDC, urine AFB positive. Which Mycobacterial pathogen do you think will be speciated?
- A) Mycobacterium tuberculosis complex species Mycobacterium tuberculosis
B) Mycobacterium tuberculosis complex species Mycobacterium bovis
C) Non-tuberculous Mycobacterium species Mycobacterium abscessus
D) Non-tuberculous Mycobacterium species Mycobacterium avium



Case

❑ TB risk factors

- Born in India and immigrated to Canada in 1978
 - No known history of TB/contacts
- Hospital contact of TB case in ICU at Vancouver General Hospital (Oct 2012)
 - T-spot and follow-up recommended
 - No records of this

❑ Background history

- August 2019 – Diagnosed with high-risk non-muscle invasive bladder cancer
 - Transurethral Resection of Bladder Tumour (TURBT)
 - Given BCG from November 2019 – March 2021 (induction and two rounds of maintenance)
- Recurrence → gemcitabine for 1 year until 2022
- Repeat TURB in 2023 showed recurrence
 - Patient declined radical cystoprostatectomy and ilial conduit
- Mitomycin intravesical instillation instead

Case

Illness course

☐ 5 October 2023

- Midstream urine AFB smear and culture:
 - AFB seen
 - Confirmed to be *Mycobacterium bovis* “BCG strain”
 - Attempted to manage as an outpatient
 - Ultimately readmitted with failure to cope at home “weakness, decline”

- CT chest:
 1. **Multiple new random bilateral 1-4 mm solid pulmonary nodules.** These raise concern for infection, including mycobacterial infection and fungal infection. Differential would include metastases.
 2. New **mild focal centrilobular nodules in the posterior segment of the right upper lobe** in keeping with infectious bronchiolitis.
 3. Small nodular foci of consolidation and centrilobular nodules in the right lower lobe have resolved.

Case



Test	Results
Leukocyte	7.3 x10 ⁹ /L
Hemoglobin	77 g/L
Platelets	233 x10 ⁹ /L
Creatinine	197 x10⁹/L (2.23 mg/dl)
Liver enzymes	
Alanine aminotransferase	22
Gamma-glutamyltransferase	27
Alkaline phosphatase	78
Total bilirubin	6
Urinalysis	Moderate leukocytes and moderate blood
Urine culture	No growth
Blood culture	No growth
C-reactive protein	90 mg/L
Prostate Specific Antigen	Negative

Case

☐ 4 Oct 2023

- Blood AFB culture collected
- Planned for outpatient bronchoscopy within the next 2 weeks
- Started on Isoniazid, Ethambutol, Rifabutin, Pyridoxine
- Discharged



Case



□ 15 Oct 2023

- Readmitted within two days with inability to care for self
- Undergoes bronchoscopy:
 - 4+ AFB positive – Mycobacterium tuberculosis complex positive/PCR positive for M. bovis BCG strain
- AFB blood culture also positive
 - Mycobacterium tuberculosis complex positive/PCR positive for M. bovis BCG strain

Question 3

Have you ever seen a patient with Disseminated BCG-osis infection following solid organ transplant?

- A) Yes
- B) No



Bacillus Calmette-Guerin “BCG”



Review

Bacillus Calmette-Guerin “BCG”

- ❑ Live attenuated strain from *Mycobacterium bovis*
- ❑ Currently, BCG is used in immunization and bladder cancer treatment
- ❑ Developed by Calmette and Guerin and was first administered in 1921
- ❑ Several daughter strains from the parental BCG strain were developed

Miyazaki, J., Onozawa, M., Takaoka, E., & Yano, I. (2018). Bacillus Calmette–Guérin strain differences as the basis for immunotherapies against bladder cancer. *International Journal of Urology*, 25(5), 405–413. <https://doi.org/10.1111/iju.13538>

Review

BCG and Bladder Cancer

- ❑ Used in the treatment of non-muscle invasive bladder cancer (NMIBC)
 - Carcinoma in situ (CIS)
 - Ta stage
 - T1 stage

- ❑ Gold standard management is removal of via transurethral resection (TUR) followed by Intravesical BCG treatment

- ❑ Regimen
 - Induction: weekly for 6 weeks
 - Maintenance: 1 year (once per week for three weeks at 3, 6, and 12 months after the initial BCG treatment)

Miyazaki, J., Onozawa, M., Takaoka, E., & Yano, I. (2018). Bacillus Calmette–Guérin strain differences as the basis for immunotherapies against bladder cancer. *International Journal of Urology*, 25(5), 405–413. <https://doi.org/10.1111/iju.13538>

Review

BCG and Bladder Cancer

- ❑ Meta-analyses of randomized trials have shown that intravesical maintenance BCG after TUR reduced the recurrence rates significantly, and BCG significantly reduces the risk of progression to muscle invasive disease after TUR in patients who receive maintenance BCG
- ❑ Randomized prospective study compared standard surgical therapy with standard surgical therapy plus BCG in a group of 37 patients with superficial bladder cancer. Among the control patients, 42% had tumor recurrence in the follow-up period compared with 17% treated with BCG (P = 0.029)
- ❑ Randomized trial, patients with recurrent bladder tumors or carcinoma in situ were randomly assigned to receive either doxorubicin or intravesical BCG. For patients with carcinoma in situ, the probability of a complete response was 34% for doxorubicin and 70% for BCG (P < 0.001)
- ❑ Meta-analysis, 32% reduction in the risk of recurrence after BCG immunotherapy compared to Mitomycin C immunotherapy

Miyazaki, J., Onozawa, M., Takaoka, E., & Yano, I. (2018). Bacillus Calmette–Guérin strain differences as the basis for immunotherapies against bladder cancer. *International Journal of Urology*, 25(5), 405–413. <https://doi.org/10.1111/iju.13538>

BCG and Bladder Cancer

- ❑ Pathogenesis and mechanism of action
 - Not fully understood
 - Attachment of live BCG to the urothelium and infecting cancer cells
 - Recruitment of immune cells to the area and then urinary release of cytokine
 - Introduction of anti-tumour effect

Systematic review on oncologic outcomes on adjuvant endovesical treatment for non-muscle invasive bladder cancer in patients with solid organ transplant

Matthieu Simonet¹ · Ana Dominguez Gutierrez² · Angelo Territo³ · Thomas Prudhomme⁴ · Ricardo Campi⁵ · Iulia Andras⁶ · Michael Baboudjian¹ · Vital Hevia² · Romain Boissier^{1,7}  · For the Young Academic Urologist (YAU) E. A. U. Group of Renal Transplantation

- ❑ Medline search for relevant publications in SOT
- ❑ 23 retrospective studies with 238 patients
 - 206 kidney transplants, 5 liver, 2 heart
 - 19% received BCG, 22% chemotherapy, 59% TURBT alone
- ❑ Recurrence
 - 65% BCG, 36% chemotherapy, 40% TURBT alone

Simonet M, Dominguez Gutierrez A, Territo A, Prudhomme T, Campi R, Andras I, Baboudjian M, Hevia V, Boissier R; Young Academic Urologist (YAU) E. A. U. Group of Renal Transplantation. Systematic review on oncologic outcomes on adjuvant endovesical treatment for non-muscle invasive bladder cancer in patients with solid organ transplant. *World J Urol.* 2022 Dec;40(12):2901-2910. doi: 10.1007/s00345-022-04188-9. Epub 2022 Nov 11. PMID: 36367586.

Review

BCG - Adverse events

- ❑ In a more recent report on European Organization for Research and Treatment of Cancer (EORTC) trial 30911, 19% of patients who accepted intravesical BCG had to stop the treatment because of complications, and only 29% completed the 3-year immunotherapy

Genitourinary complications	Incidence (%)	Systemic complications	Incidence (%)
Cystitis	27-95	Fever (>38.5°C)	2.9
Bladder contracture	< 1	Mycotic Aneurysms	0.7-4.6
Bladder ulceration	1.5	Miliary pulmonary tuberculosis	0.4
Penile lesions*	5.9	Granulomatous hepatitis	0.7-5.7
Tuberculous epididymo-orchitis	0.4	Reactive arthritis	0.5-5.7
Symptomatic prostatitis	10	Tuberculous Spondylitis	3.5
Ureteral obstruction	0.3	BCG sepsis	0.4
Kidney infections	0.3-3.5		

*Penile lesions consisted of nodules, papules, plaques, or ulcers, with or without inguinal lymph node enlargement.

Review – BCG Genitourinary Complications

Genitourinary complications	Initial therapy	Auxiliary treatment	BCG adjustment
Cystitis (irritative voiding symptoms > 48 hours or intolerable)	Spasmolytics, anticholinergics or nonsteroidal anti-inflammatory drugs	Antibiotics administration If bacterial cystitis is diagnosed	Withheld until symptom relieves and antibiotic therapy ends
Bladder contracture	Bladder hydrodistension	Systemic steroids; Exceptionally surgery (bladder augmentation or cystectomy)	Discontinue for decreased bladder capacity
Bladder ulceration	300 mg isoniazid and 600 mg rifampin daily for 6 months	None	Withheld until resolution of the bladder lesion and BCG negative urine
Granulomatous balanitis	Various combinations of isoniazid, ethambutol or rifampin for 6 to 12 months	None	Withheld until the lesion resolves
Tuberculous epididymo-orchitis	300 mg isoniazid and 600 mg rifampin daily for 3 to 6 months	For isoniazid resistance, fluoroquinolones or an anti-TB aminoglycoside; For lesion refractory to anti-TB therapy, scrotal exploration and epididymo-orchietomy	No further BCG
Symptomatic prostatitis	300 mg isoniazid and 600 mg rifampin daily for 3 to 6 months	Antibiotics (fluoroquinolones) as necessary; Surgical drainage for abscess; Biopsy if no improvement on medication	No further BCG
Ureteral obstruction	300 mg isoniazid and 600 mg rifampin daily for 3 to 6 months	A temporary drainage (ureteral stenting or percutaneous nephrostomy) for hydronephrosis despite conservative therapy	Withheld when onset hydronephrosis; May resume after resolution
Kidney infections	300 mg isoniazid, 600 mg rifampin and 1200 mg ethambutol daily for 6 months	Biopsy if no response to medical treatment	No further BCG

Liu, Y., Lu, J., Huang, Y., & Ma, L. (2019). Clinical Spectrum of Complications Induced by Intravesical Immunotherapy of Bacillus Calmette-Guérin for Bladder Cancer. *Journal of Oncology*, 2019, 6230409–6230411. <https://doi.org/10.1155/2019/6230409>

Review – BCG systemic complications

Systemic complications	Initial therapy	Auxiliary treatment	BCG adjustment
Fever (>38.5°C for more than 48 hours)	300 mg isoniazid, 600 mg rifampin, and 1200 mg ethambutol daily for at least 3 months. Plus an empirical non-specific antibiotic to cover Gram-negative bacteria and/or <i>Enterococcus</i> with or without steroids.	Treatment adapted to urine culture results.	No further BCG
Mycotic Aneurysms	300 mg isoniazid, 600 mg rifampin and 1200 mg ethambutol daily for 12 months	Surgical resection of aneurysms and revascularization (eg extra anatomic bypass or in situ replacement)	No further BCG
Miliary pulmonary tuberculosis	A variety of combined isoniazid, ethambutol, streptomycin, or rifampin for 6 to 12 months	None	No further BCG
Granulomatous hepatitis	300 mg isoniazid, 600 mg rifampin and 1200 mg ethambutol daily for 6 months	None	No further BCG
Reactive arthritis	Non-steroidal anti-inflammatory drugs ± corticosteroids	Disease-modifying antirheumatic drugs (methotrexate) and/or isoniazid for severe or unimproved cases	BCG can be resumed after benefit-risk assessment till resolution of symptoms; Dose reduction should be considered
Tuberculous Spondylitis	Combined isoniazid, rifampin and ethambutol for 9 to 12 months Emergency admission and intensive care;	Surgical intervention for further complications	No further BCG
BCG sepsis	300 mg isoniazid, 600 mg rifampin and 1200 mg ethambutol daily for 3 to 6 months; Intravenous 40 mg prednisolone should be given initially and oral steroids taper gradually	Broad-spectrum antibiotics as needed	No further BCG

Liu, Y., Lu, J., Huang, Y., & Ma, L. (2019). Clinical Spectrum of Complications Induced by Intravesical Immunotherapy of Bacillus Calmette-Guérin for Bladder Cancer. *Journal of Oncology*, 2019, 6230409–6230411. <https://doi.org/10.1155/2019/6230409>

Question 4

In a solid organ transplant patient with a diagnosis of bladder cancer, you are asked whether Urology can proceed with Intra-vesical BCG therapy, would you recommend proceeding?

- A) Yes
- B) Yes, but give patient prophylaxis
- C) No



Review

Predisposing factors

❑ Immunosuppression

- In the largest case series of 45 immunosuppressed patients BCG therapy was found well-tolerated, and no BCG sepsis was reported
- European Association of Urology (EAU) guideline suggests that BCG should be used with caution in immunocompromised patients, despite the comparable incidences of BCG-induced complications reported between patients with and without immunocompromised status

❑ Geriatric patients

Liu, Y., Lu, J., Huang, Y., & Ma, L. (2019). Clinical Spectrum of Complications Induced by Intravesical Immunotherapy of Bacillus Calmette-Guérin for Bladder Cancer. *Journal of Oncology*, 2019, 6230409–6230411. <https://doi.org/10.1155/2019/6230409>

Review

Prevention

- ❑ Administer BCG at minimum 2 weeks after TUR

- ❑ Dose of Intra-vesical BCG does not matter
 - In a randomized prospective study, the percentage of no local toxicity in 248 patients with reduced dose of 27 mg intravesical BCG was significantly lower than that in 252 patients with standard dose of 81 mg (33.3% vs. 45.3%) with similar outcomes for recurrence and progression, but the differences in severe systemic toxicity were not significant between reduced dose arm (4.4%) and standard dose arm (3.6%)

 - However, in a more recent study of 1316 patients, one-third dose was compared to a full dose of BCG given for 1 year or 3 years, and no significant differences in side effects were detected according to dose or duration of BCG treatment in the four arms

Review

Prevention

☐ Prophylaxis

- There are studies looking at antibiotic prophylaxis.
 - Reduced side effects shown with prophylaxis prulifloxacin
 - Isoniazid trial negative
- Minimal data on impact of effectiveness of therapy

Review

Isolation and contact tracing

- For the 6 hours post treatment, patients should sit down when urinating and clean their hands and genital area well with soap and water
- For the 6 hours post treatment, the toilet bowl may be disinfected after voiding by adding 1-2 cups of liquid household bleach to the toilet bowl and waiting for 15 minutes before flushing
- To protect their partner, patients are advised to either refrain from intercourse or use a condom for one week after BCG treatment
- Technically part of the TB complex
- 2022 Canadian TB Standards silent on BCG
- Airborne isolation was implemented for our patient

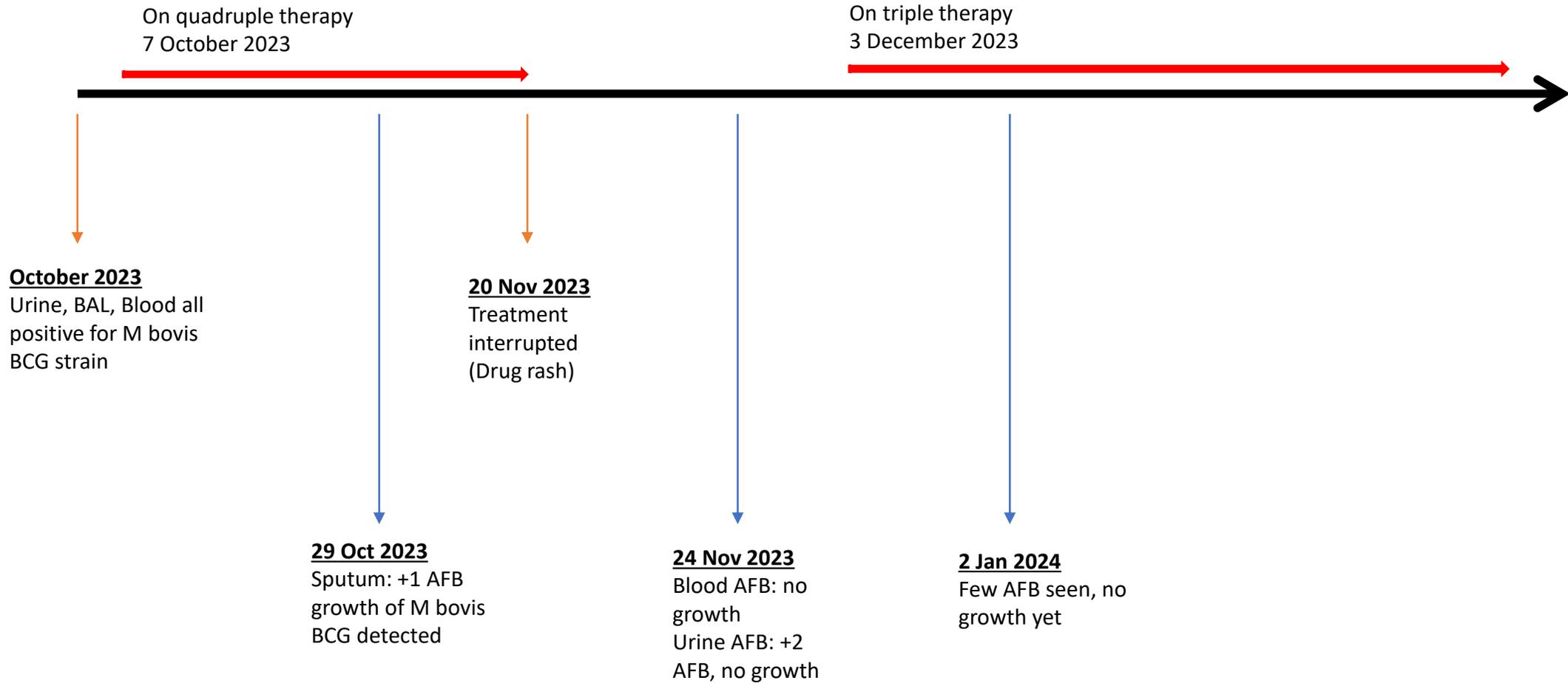
Case

Back to the patient

- ❑ Discharged on Isoniazid, Ethambutol, Rifabutin, Levofloxacin, Pyridoxine - 7 October 2023
- ❑ Six weeks later, seen in clinic with drug rash, and Achilles tendinopathy bilaterally – sequential drug introduction
- ❑ After Ethambutol introduction, rash within 3 days
- ❑ Tolerated Isoniazid, Rifabutin, Linezolid, Pyridoxine - 3 December 2023
- ❑ By the end of December, cytopenia's secondary to linezolid
- ❑ Ultimately, transitioned to Isoniazid, Rifabutin, Clofazimine, and Pyridoxine
- ❑ Further work up pelvic adenopathy and previously identified prostate nodule → likely cancer with metastases
 - Feeding tube for weight loss
 - Ongoing poor functional status
 - Palliative care involved

Case

Back to the patient



Case

- ❑ Unusual aspects of the case
 - BCG diagnosis is remote from instillation
 - Not classic BCGosis case
 - Duration of infection

- ❑ BCG is culture positive from respiratory specimens
 - Not a hypersensitivity reaction
 - Transmission more likely, but management unclear

Acknowledgments

- Dr Alissa Wright – Transplant ID
- Dr Allison Mah – Transplant ID
- Dr Sara Belga – Transplant ID
- Dr William Connors – General ID/TB
- Tanveer Brar – Lung Transplant Pharmacist

Thank you

Comments or Questions

