









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Breeching “The Goldilocks Zone”: Tetraplegia as a Rare Life-Altering Infective Complication of Adjuvant Breast Cancer Chemotherapy

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ABSTRACT

Background: Adjuvant chemotherapy has been an integral component of breast cancer care for decades. Advances in supportive care have been made, but despite this, infective complications of therapy remain a significant toxicity concern.

Case Presentation: A premenopausal patient presented to the emergency department during the third wave of the Covid-19 pandemic with sepsis after a second course of adjuvant docetaxel-cyclophosphamide chemotherapy. Overnight she developed tetraplegia. An urgent MRI cervical spine revealed a pre-vertebral, vertebral, and epidural abscess. This was treated with an emergency C4-C7 posterior cervical laminectomy and decompression. Her inpatient care involved a protracted ICU admission followed by rehabilitation. She remains tetraplegic and requires continued inpatient care over a year after presentation. Restricted pandemic-related hospital visiting has compounded the impact of her illness.

Conclusion: Infective complications of adjuvant breast cancer chemotherapy remain an issue despite advances in supportive care. This case highlights the devastating, life-altering impact that these complications can have as emphasized by the inclusion of the patient’s perspective.

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INTRODUCTION

The Goldilocks Zone is a concept of biological optimization in which “not too much” and “not too little” treatment is given.¹ In the context of early-stage breast cancer care, too little treatment can result in potentially preventable relapse, whilst too much treatment can result in impaired quality of survival and excessive treatment related toxicity.^{2,3} Adjuvant

chemotherapy in early-stage breast cancer was initially developed by Bonadonna and colleagues to improve breast cancer outcomes after surgery.⁴ Multiple cycles of poly-chemotherapy regimens such as docetaxel-cyclophosphamide (TC) are now commonly used.⁵ However, infective complications of therapy have always been a significant toxicity concern.⁶⁻¹⁰ These concerns have led to efforts to define The Goldilocks Zone for these patients with the use of pathology and genomic platforms to identify patients who do not need chemotherapy along with hematologic growth factor support and digital therapeutics to help those who do.¹¹

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Despite these developments, adjuvant chemotherapy remains a significant cause of patient morbidity and mortality. We present a case of tetraplegia due to a spinal abscess complicating adjuvant TC chemotherapy which occurred during a national lockdown due to the third wave of the Covid-19 pandemic in Ireland. This case report highlights a rare complication of a common treatment and reinforces the negative impact which the Covid-19 pandemic has had on patient care.

CASE PRESENTATION

A 48-year-old premenopausal female without any prior significant medical history presented with a symptomatic right breast cancer which was initially treated with breast conserving surgery.

Post-operative pathology demonstrated an invasive ductal carcinoma grade 3, 2.8cm, with isolated tumor cells noted in 1 of 2 sentinel nodes. The immune-profile assessment revealed the tumor was estrogen and progesterone receptor positive and the HER2 score was 0. Oncotype assessment was performed. A score of 37 indicated a 25% distant recurrence risk with 5 years of hormone therapy and greater than 15% absolute benefit from chemotherapy. Consequently, four cycles of TC chemotherapy with growth factor support was prescribed. Adjuvant chemotherapy was to be followed by radiotherapy and hormone therapy for 5 years.

The first cycle of chemotherapy was completed with the patient only experiencing mild side effects. Twelve days after completing her second cycle of chemotherapy, she presented to the emergency department with a 5-day history of malaise, generalized myalgia, anosmia, ageusia, headaches and neck stiffness. Importantly, this presentation occurred during the third wave of the Covid-19 pandemic in Ireland and a national lockdown. In an effort to continue cocooning, the patient presented to the emergency department two days after her first recorded fever.

Vital signs on presentation were abnormal with a heart rate of 150 beats per minute and a temperature of 38 degrees Celsius. Oxygen saturations were 99% on room air and the patient was initially normotensive.

Admission blood tests revealed a white cell count of $38.4 \times 10^9/L$, haemoglobin of 11 g/dL, platelets of $34 \times 10^9/L$ and an elevated C-reactive protein of 395.6 mg/L.

The initial impression was that this could potentially be a case of Covid-19 given the nature of the symptoms. Ceftriaxone and intravenous fluids were commenced. SARS COV-2 testing continued to be negative.

Her condition deteriorated within two hours of arrival with blood pressure declining to 85/63 mmHg. Despite multiple fluid boluses, her blood pressure failed to respond and inotropic support was commenced. In response to this clinical deterioration, vancomycin and gentamicin were added to her antimicrobial treatment.

On day two of hospitalization, cross-sectional imaging demonstrated multifocal pneumonia (Figure 1) and hyper-enhancement of the adrenal gland suggestive of a hypo-perfusion complex. Ceftriaxone was switched to piperacillin-tazobactam.

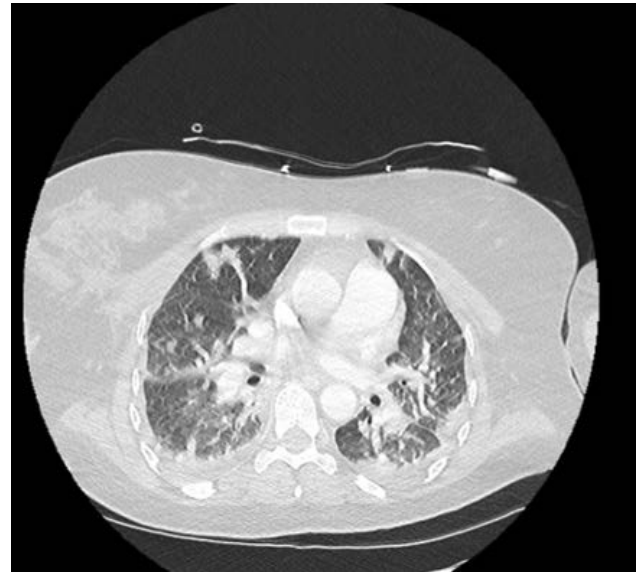


Figure 1. Admission CT-Thorax demonstrating multifocal airspace opacities in keeping with multifocal pneumonia. The quality of the images is unfortunately affected by respiratory motion artefact.

The patient was transferred to the intensive care unit due to increasing oxygen requirements and persisting hypotension despite inotropic support. She was commenced on AIRVO in an effort to maintain oxygen saturations. Gram positive cocci were isolated in the aerobic blood culture.

On day three of hospitalization, the patient lost power in both lower limbs. An urgent MRI cervical spine revealed a pre-vertebral, vertebral, and epidural abscess with anterior and posterior components from C2-T1 with resultant moderate narrowing of the central canal and cord compression from C5-C7 (Figure 2). The patient was intubated on day three and underwent an emergency C4-C7 posterior cervical laminectomy and decompression. Post-operatively, upper limb examination confirmed reduced power with shoulder abduction and elbow flexion being scored as 4/5 bilaterally while elbow extension was scored as 3/5 bilaterally. Power distally was scored as 0/5 in both upper limbs. Tone, reflexes and sensation were all documented as normal. Neurological



examination of the lower limbs revealed persistent 0/5 power throughout all muscle groups bilaterally.

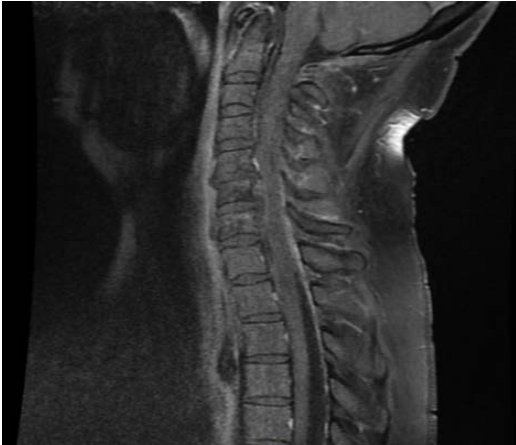


Figure 2. The initial MRI Cervical Spine revealing a pre-vertebral, vertebral, and epidural abscess with anterior and posterior components from C2-T1.

Antimicrobial therapy was tailored to introduce flucloxacillin on day four. Blood cultures from day 1, day 2, and day 5 all isolated staphylococcus aureus and bone fragments from theatre specimens taken on day 3 also grew staphylococcus aureus (MSSA). In view of ongoing critical illness and for putative anti-toxin effect, clindamycin was added and further investigations were performed to isolate potential sources of infection. A trans-esophageal echocardiogram was performed which was negative for infective endocarditis.

On day four of admission, the patient was extubated. She remained on high-flow oxygen with reducing inotropic support. A repeat MRI cervical spine demonstrated less pronounced but persistent abnormal cord signal. Oedema of the C5 and C6 vertebral bodies was again demonstrated - consistent with osteomyelitis (Figure 3).

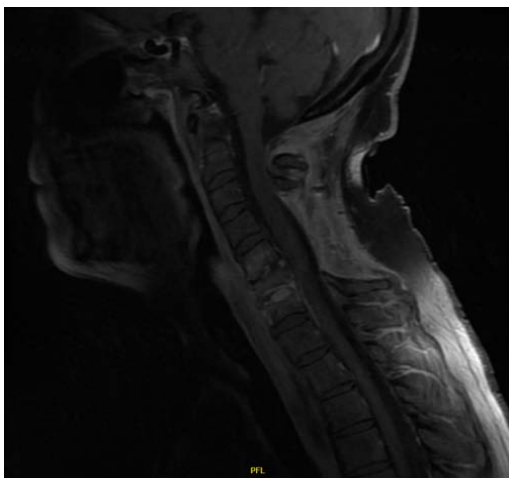


Figure 3. Repeat MRI Cervical Spine post eight weeks of antibiotics demonstrating persisting osteomyelitis (T1 fat suppressed sagittal view of the C spine, post IV contrast).

In view of the documented oedema, she was placed on intravenous dexamethasone.

On day six, the patient started to develop increasing oxygen requirements and hemoglobin dropped from 8.9g/dL to 7.4g/dL. A bedside echocardiogram was normal. Due to respiratory distress, the patient was re-intubated. Blood cultures became sterile on day seven.

The patient's time in ICU was protracted requiring multidisciplinary input, intravenous antibiotic therapy and surgical assessments. Multidisciplinary care included anesthetics, rehabilitation medicine, neurosurgery, physiotherapy, occupational therapy, speech and language therapy and social work.

A tracheostomy was placed on day thirteen and she was weaned from ventilator support. On day twenty, the patient was reviewed by the rehabilitation services.

A repeat MRI cervical spine performed on day fifty-nine demonstrated persistent osteomyelitis from the C5-C7 levels despite 8 weeks of intravenous flucloxacillin. Following discussion with microbiology colleagues, it was decided to give rifampicin and doxycycline for a further twelve weeks. On day 107 she was transferred to the National Rehabilitation Hospital. Follow up imaging on day 134 revealed bony consolidation at C6-C7 in keeping with healing following a treated osteomyelitis. Adjuvant breast radiotherapy was completed, and hormonal therapy was initiated.

At present, 18 months post initial presentation, she remains a hoist transfer and mobilizes with a powered wheelchair. She requires assistance in all personal activities of daily living. After her initial presentation to hospital in February 2021, it is estimated that she will not get home until Autumn 2022. Discharge arrangements are compromised due to community staff shortages following the COVID-19 pandemic.

PATIENT PERSPECTIVE

Towards the end of 2020, I found a lump in my breast. The lump was removed the following month and I started chemotherapy in the New Year. The whole process was a lot harder on my husband as he could not come into the hospital with me for appointments because of the Covid-19 pandemic. I have two children with additional needs; one of my sons has ADHD with dyspraxia and is currently doing his Leaving Certificate and my other son is on the autism spectrum.

Chemotherapy had been going well and I had minimal side effects. Things changed on the 7th of February 2021. I cannot recall exactly what we were doing that Sunday but I remember finding it difficult to climb the stairs at home. My husband decided to call for an ambulance. Overall, I remember little of



ICU. I do remember my oncologist coming into ICU every evening and standing at the end of the bed. I could not talk so they had to put a small tube in my neck so that I could say a few words. Due to Covid-19, my family could not come into ICU to visit.

After ICU, I was transferred to a rehabilitation hospital. I was turned every 3 hours for 6 weeks even during the night in a bid to prevent bed sores. It was impossible to sleep, and every movement was excruciating even with painkillers. I would have to be showered on a trolley. Initially I was not able to feel from my chest down. First, the toes on my left leg started to move. At Christmas, my left leg started to kick out and then the toes on my right leg started moving. I can feel reflexes and the water on my legs now. I am still a full hoist transfer. The toughest thing is the wheelchair; I cannot get my head around the idea of it and it is very hard to stay positive. The catheter does not bother me, but my bowels are also tough to manage. When I was in the rehabilitation hospital, I needed an enema every second day as well as manual stimulation. It could take up to two hours for me to open my bowels even with that. Yesterday, I passed in forty minutes, and this was one of my best days.

I think of my boys as much as myself and the pandemic did not make things easier. At Christmas, I was still in the rehabilitation hospital, and I could not go home. The doctor was able to let me out for a dinner in a restaurant with my family before Christmas. The night before, however, I was a close contact of a confirmed Covid-19 case and so I had to be swabbed and I almost could not go to dinner. Christmas was very hard. After fourteen months in hospital, my main aim now is to get home. Trying to manage everything for my boys has been challenging from hospital. I have a plan in my head, and I have my own exercises to do. My boys would not be able to help me do my stretching but reflexology, tilt tables and acupuncture might help. The house is fully set up. We have a bedroom downstairs with an adjoining wet room. There is a ramp into the room and the kitchen door has been widened. To go home I need a morning visit, two visits in the afternoon to help empty my catheter and one in the evening. I hope that, when I go home, I will adjust but we will have to see. My focus is on getting home to my boys, but admittedly I have thought about whether I might have been better off if I did not wake up in ICU.

DISCUSSION

This case highlights a devastating, quality-of-life altering, infective complication of adjuvant breast cancer chemotherapy in an otherwise previously healthy patient.

While the patient had tolerated her first course of chemotherapy well and had received prophylactic growth factor support to reduce the risk of infective complications, she became unwell during the second course and remains in hospital 15 months after presentation.

This case emphasizes the importance of infective complications in contemporary breast cancer care. This complication occurred despite significant advances in supportive measures and in clinician experience in the selection of patients for cytotoxic chemotherapy. It is a cautionary tale for our community.

In the present case, primary prophylactic support was used to reduce the risk of infective complications from TC therapy. Do *et al.* had previously reported a 23.3% risk of febrile neutropenia with the TC regimen particularly in patients older than 65 years.⁹ Higher rates have been noted in observational studies.¹² Primary prophylaxis reduces this risk by 92%. With the onset of the COVID-19 pandemic, concern was raised that these agents could increase lung damage in infected patients.¹³ Nonetheless, many guideline groups recommended their more widespread use in patients receiving cytotoxic chemotherapy to reduce their risk of hospitalisation during this time.¹³⁻¹⁵ In the present case, common side effects from these agents and from TC chemotherapy such as myalgia, arthralgia and bone pain may have masqueraded symptoms of sepsis.

Spinal epidural abscesses (SEA) are relatively rare with an incidence of approximately 1.2 per 10,000 patients. Potential risk factors include diabetes mellitus, immunosuppression, malignancy, trauma, and drug use.¹⁶ Although rare, once present they have the potential to cause permanent neurological deficits and can be devastating for patients and their families. Early diagnosis is essential in preventing permanent disability, but diagnostic delays can often occur.¹⁷ The development of paralysis was masked by septic shock requiring intensive care admission, inotrope, and respiratory support. Prompt assessment and onset of neurosurgical intervention was possible due care in a hospital where a Cancer Center and Level 1 Trauma Center are co-located with onsite neurosurgical expertise. Only 3 of 8 national cancer centers in Ireland have these onsite resources. The critical nature of the patient's illness would have precluded inter-hospital transfer.

At the time of presentation, Ireland was in a national lockdown and experiencing the 3rd wave of the COVID-19 pandemic. A national vaccination program had been initiated prioritizing health care workers and the elderly. Patients receiving cytotoxic chemotherapy were encouraged to limit contacts to avoid infection and to maintain chemotherapy dose



intensity. Previous studies had focused on the impact of lockdown on delayed cancer diagnosis; however, this case highlights the impact of lockdown on dealing with the complications of cancer therapy.¹⁸⁻²⁰ While the impact of the pandemic has reduced in the ensuing year, many patients with cancer remain vulnerable to COVID-19 despite vaccination. Social distancing measures, particularly while undergoing cytotoxic chemotherapy, remain necessary.²¹ The vulnerability highlighted in this case report remains and highlights the potential importance and role of telemedicine supplementation to standard of care practice.²²

The integration of the patient's testimony into this report reinforces the importance of the patient's voice and provides us with a salutary lesson. While the patient ultimately survived, her and her family's lives have been forever changed by the events of her admission. Her reality emphasizes the need for

continued progress in decision making processes for adjuvant breast cancer therapy, and for safer less toxic therapeutic options for patients.

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CONFLICTS OF INTEREST

None declared.

ETHICAL CONSIDERATIONS

Informed consent for publication was obtained from the patient.

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