IDCases 36 (2024) e01947

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

Case report

Candida parapsilosis bone marrow infection in an immunocompetent patient

Nicholas James Edwards [a,b], Paul Bao Duy La [a], Joshua Haron Abasszade [a,c], Timothy Abrahams [a], Kirollos Nan [a], Alistair John Tinson [c,d], Aditya Tedjaseputra [e], Min-Ne Wu [a,*]

[a] Department of General Medicine, Monash Health, Clayton, Victoria 3168, Australia
[b] Department of Emergency Medicine, Western Health, Footscray, Victoria 3011, Australia
[c] Department of General Medicine, Northern Health, Epping, Victoria 3076, Australia
[d] Department of General Medicine, Austin Health, Heidelberg, Victoria 3084, Australia
[e] Monash Haematology, Monash Health, Clayton, Victoria 3168, Australia

ARTICLE INFO

Keywords:
Bone Marrow
Candida parapsilosis
Invasive Fungal Infections

ABSTRACT

Background: We discuss a case of an immunocompetent patient who presented with fever and tachypnoea, found to have *Candida parapsilosis* bone marrow infection, cultured on bone marrow aspirate sample. *Candida parapsilosis* is an opportunistic yeast pathogen that typically affects immunocompromised individuals, or occurs in patients with apparent introduced source; neither of these factors were present for this case. Bone marrow aspirates and trephines are not regular investigations for fever; however they can be useful diagnostic aids as evidenced in this case.

Case report: An 83-year-old woman presenting with fevers and tachypnoea was being treated for a systemic bacterial infection, however was unresponsive to empirical antibiotic therapy. To exclude an occult malignancy, an 18-fluorodeoxyglucose positron emission tomography scan was conducted. Significant bone marrow uptake was noted, prompting a bone marrow aspirate and trephine to investigate for a hematological malignancy. While the trephine biopsy was benign, a culture of the aspirate grew *Candida parapsilosis*. Intravenous antifungal therapy was initiated; however, the patient did not improve despite targeted therapy likely due to delays in diagnosis, and was palliated.

Conclusion: Our case seeks to demonstrate a novel case whereby a bone marrow aspirate culture provided a conclusive diagnosis of invasive *Candida parapsilosis* bone marrow infection, and guided treatment in an immunocompetent patient. It is important for clinicians to consider invasive fungal infections in febrile patients regardless of immune status. Additionally, when performing a bone marrow aspirate and trephine on a febrile patient, we recommend including aspirate fungal cultures to investigate for an invasive fungal infection.

Background

Invasive fungal infections are an important diagnostic consideration within the subset of immunocompromised patients, with typical risk factors including immunodeficiency, immunosuppressive therapy, diabetes, invasive procedures and devices [1–3]. Most of these infections are found in patients with a significant immune response deficit, as opposed to immunocompetent or minimal risk patients [2]. Investigations for an invasive fungal infection may also be considered in cases where there is ongoing deterioration in a patient's condition despite appropriate antibiotic usage, and there is an increasing suspicion of an atypical source of infection.

Candida parapsilosis is an opportunistic yeast species that is becoming increasingly prevalent as a source for nosocomial infection and is a commensal microbe on 19% of health-care workers hands [2]. The fungus has the potential to be transmitted to patients especially in the context of an invasive procedure, particularly in cases of parenteral nutrition and prosthetic insertion [2]. *Candida parapsilosis* is detected in 16.5% of candidiasis infections [4], and is the causal agent for 17–19% of candidemias [1,2]. Important invasive presentations of *Candida parapsilosis* include fungaemia, meningitis, endocarditis, and peritonitis [2].

To our knowledge, there is a paucity in the current literature regarding the use of bone marrow (BM) aspirates to detect *Candia*

* Correspondence to: Department of General Medicine, Monash Health, 246 Clayton Road, Clayton, Victoria 3168, Australia.
E-mail address: minne.wu@monashhealth.org (M.-N. Wu).

https://doi.org/10.1016/j.idcr.2024.e01947
Received 5 October 2023; Received in revised form 26 March 2024; Accepted 14 April 2024
Available online 15 April 2024

parapsilosis mycoses in immunocompetent patients who have positron emission tomography (PET) avidity. There is only one other documented case of a solitary BM mycosis in a patient with neither acquired immunodeficiency nor immunomodulating therapy, however no BM aspirate culture was taken in that case and the diagnosis was determined through a combination of BM trephine histology and detection of serum antifungal antibodies [5]. Here we describe a case whereby the concomitant use of a PET scan with a BM aspirate culture allowed for targeted therapy to be initiated.

Case report

An 83-year-old woman was transferred to an Australian tertiary hospital after a mechanical fall. On presentation, she was febrile with a temperature of 40.1 °C, tachypnoeic at 28 breaths per minute, tachycardic at 112 beats per minute, and had a blood pressure 123/53 mmHg. Pulse oximetry saturations were 94% on 3 L/min oxygen via low-flow nasal cannula. Her past medical history was significant for hypertension, hypercholesterolemia and type 2 diabetes mellitus (T2DM) with a hemoglobin A1c (Hba1c) of 70 mmol/mol (20−42), without any macrovascular or microvascular complications. She had neither acquired nor inherited immunodeficiency, was not on immunosuppressive medication and had no history of malignancy or transplantation. The patient had no recent history of penetrating trauma or surgery. She reported having lost seven kilograms in the three months prior to presentation and had an admission one month prior after a separate fall at home, from which she had a full recovery without any invasive intervention. The patient had bi-basal crepitations on chest auscultation, however there was no peripheral oedema, jugular venous pressure was not elevated and there was no shifting dullness to suggest ascites. Additionally, she denies having a cough, dysuria, diarrhea, and there was no clinical evidence of meningism or infective skin changes. Furthermore, no injuries were noted from the fall, and the patient was cleared from trauma after a tertiary survey by the general medical team.

Prior to admission, the patient was already found to be positive for respiratory syncytial virus (RSV), but negative for SARS-CoV-2 infection, on polymerase chain reaction testing. On admission, the patient had high inflammatory markers with C-reactive protein 228 mg/L (0−5), procalcitonin 0.66 μg/L (0.00–0.07), ferritin 528microg/L (30−310), and fibrinogen 5.9 g/L (1.5–4.0). She had a microcytic anemia with a hemoglobin of 98 g/L (110−160), mean corpuscular volume of 72 fL (78−98). White cell count, platelet count, and urea were normal. A creatinine of 94 μmol/L (45−90) was raised from baseline 57 μmol/L. The patient was hypokalemic with potassium of 3.2 mmol/L (3.5–5.2). Initial cultures of blood, urine and sputum were sterile, including a set taken prior to commencement of any antibiotics and antifungals. Throughout admission, a further eleven blood and two urine cultures were taken, all of which were sterile. Human immunodeficiency virus, hepatitis B, hepatitis C, cytomegalovirus serologies, and Legionella urinary antigen testing were all negative. Epstein-Barr virus serology was consistent with a previous infection. Serum testing for latent tuberculosis via a QuantiFERON gold test was also negative. Blood and urine cultures taken during the previous admission were all sterile, and the treating clinicians had no suspicion of a systemic infection.

A computed tomography (CT) scan of the chest revealed a lone pulmonary nodule, and moderate bilateral pleural effusions. This nodule was determined to not be radiologically consistent with tuberculosis, and a right-sided intercostal catheter was inserted radiologically. Pleural fluid glucose was 18.3 mmol/L, lactate dehydrogenase 3.22μkat/L and total protein 51 g/L (60−80). According to the Light's criteria, this indicated an exudative effusion, however fluid cytology showed no malignant cells, and cultures of the fluid were negative for bacterial and fungal growth. CT imaging of the brain, abdomen, and pelvis revealed no evidence of a malignancy or any sources of infection.

Initial concerns were that the patient had a concomitant bacterial infection superimposed with the initial RSV infection. For empirical treatment, the patient received 182 mg of intravenous (IV) gentamicin as a single dose and was given 2 g IV flucloxacillin every four hours. Antimicrobial cover was broadened to IV piperacillin-tazobactam 4 g-0.5 g every six hours. However, after refractory febrile episodes and a poor response to IV antibiotics, the potential diagnosis of an occult malignancy was also explored. Serum cancer-antigen (CA)− 125 was 25kU/L (<35), CA-19 was 20kU/L (0−35), CA15–3 was 17kU/L (0−24), carcinoembryonic antigen 1.4 μg/L (0–0.5), alpha fetoprotein 1.7 μg/L (<9), and quantitative beta human chorionic gonadotropin 2 U/L (0−12). Six days after admission, a PET scan was performed, showing diffuse BM uptake (Fig. 1), consistent with reactive or proliferative disease, and the hematology team organised a bone marrow aspirate and trephine (BMAT).

BM aspiration (May-Grunwald-Giemsa stain) revealed marked hemophagocytosis with no infiltration by malignant cells or infectious organisms (Fig. 2A). Similarly, BM trephine (hemotyxlin and eosin stain) demonstrated mild-moderate hypercellularity for age with left-shifted granulopoiesis, with no excess of blasts, lymphocytes, apparent fungal elements or granuloma formation (Fig. 2B). Furthermore, immunohistochemistry with Grocott's methenamine silver and periodic acid-schiff (PAS) staining were also negative (Fig. 2C-F; positive controls included). No potassium hydroxide preparation stains were done. No yeast cells or pseudo-hyphae were noted on any of the trephine sample stains. Gram staining was negative, however after 48 h BM aspirate culture grew a fungal colony. Using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, a diagnosis of a *Candida parapsilosis* BM mycosis was established. The BMAT was performed under sterile technique, and while it is possible that the culture result was a contaminant, the *Candida parapsilosis* was considered pathogenic for invasive infection by the infectious diseases team based on clinical picture and the results

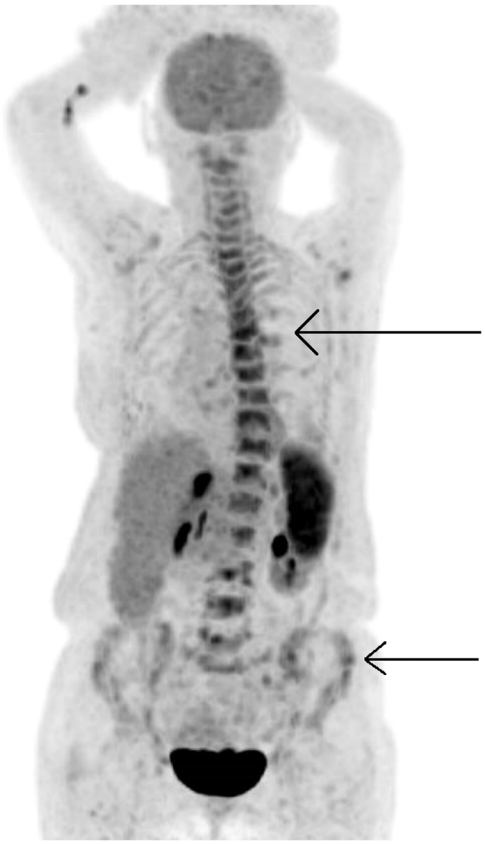

Fig. 1. PET scan showing diffuse uptake in the bone marrow of the patient. Areas of diffuse uptake indicated with arrows. PET, Positron Emission Tomography.

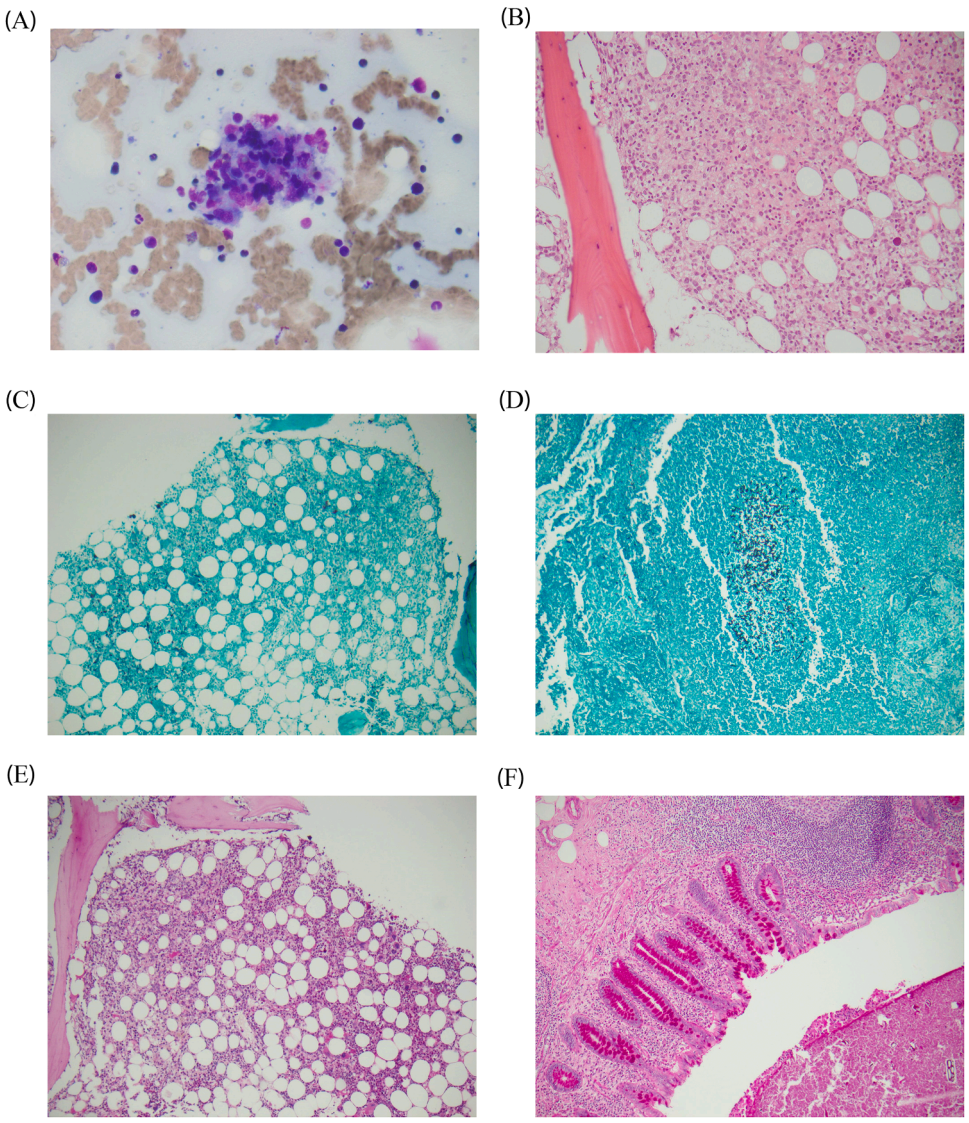

Fig. 2. Bone marrow examination findings: (A) bone marrow aspirate demonstrating hemophagocytosis with active phagocytic cells containing intact cells and cellular debris (x 400 magnification); (B) bone marrow trephine demonstrating hypercellularity with granulocytic hyperplasia and no excess of blasts, lymphocytes or granuloma formation (x 200 magnification); (C & D) bone marrow trephine immunohistochemistry with Grocott silver stain (x 100 magnification) revealed non-specific uptake only (positive control = black staining) and was negative with (E & F) Periodic acid-schiff stain also (x 100 magnification; positive control = bright pink staining).

of other negative infectious investigations. Unfortunately, the authors were not able to obtain an image of the agar plate on which the *Candida parapsilosis* colony first grew.

After the BM aspirate culture result returned on day fifteen of admission, fungal blood cultures were taken for the first time, and the patient was immediately started on IV micafungin 100 mg every 24 h. After four days, treatment was switched to fluconazole after sensitivities revealed that the *Candida parapsilosis* was sensitive to both micafungin and fluconazole. The patient received a single dose of IV fluconazole 800 mg and IV antibiotics were ceased. The patient had minimal response to the four days of targeted IV antifungal therapy and died on the nineteenth day of admission.

Discussion

The potential sources of the *Candida parapsilosis* included frequent venipuncture, several peripherally inserted venous catheters, an indwelling urinary catheter, and a single intercostal drain inserted during her admission, as well as the BMAT through which the diagnosis was made. It is also possible the patient acquired this infection during her previous stay in hospital a month prior to presentation, or she may have obtained it in the community. Notably, there was no evidence of additional cutaneous or mucosal sites of infection that may have been initial sources of candidiasis; including oral, skin, vaginal, or rectal *Candida* infection. Even with an introduced source, opportunistic pathogens usually require their host to have some level of immune dysfunction in order to thrive, before an infection becomes fulminant [3]. The patient's risk factors for developing a BM mycosis were T2DM, exposure to broad-spectrum antibiotics, and invasive procedures during admission. In patients with T2DM, the increased risk of infection becomes significant when HbA1c is greater than 69 mmol/mol [6]. The patient's HbA1c was 70 mmol/mol and her blood sugar levels ranged from 7.9–11.7 mmol/L during the time of admission. Factoring in the patient's age, this was an acceptable HbA1c and blood sugar level [6,7], and whilst the patient did have slightly increased risk of obtaining an infection, she was not treated as being immunocompromised.

In neutropenic or otherwise immunocompromised septic patients, empirical antifungals are initiated on presentation [8], however as our

patient fit neither of these criteria antifungals were started only after BM aspirate culture results returned.

The differential diagnosis of a malignancy was considered early, due to the combination of weight loss, persistent fevers, and lack of response to antimicrobial treatment. The PET scan was completed six days after admission and demonstrated diffuse uptake in the bone marrow (Fig. 1). Subsequently, there were significant concerns about a hematological malignancy or BM infection, which warranted a BMAT, that was performed on day eleven. Given that it was the aspirate culture that guided appropriate therapy, an earlier BMAT may have resulted in earlier treatment and potentially a better outcome for the patient, however it is important to appreciate the limitations of BM investigations. BM trephine biopsy has a 14–31.9% yield as a diagnosis-defining investigation [9,10], however, aspirate cultures have mixed yields ranging from 0–40% [10,11] and are not typically considered a common investigation for fevers. Blood and urine cultures have a higher diagnostic yield than BM culture when investigating for fevers [10]. There are however some reports that BM aspirate culture slightly enhances diagnosis in immunocompetent patients [12], by up to 5.5% [10]. It is worth noting that BM culture has a higher sensitivity for detecting fungal pathogens in comparison to a BM stain and microscopy, and that detecting a fungus on a BM trephine stain in an immunocompetent patient is generally rare [13].

Interestingly, serial fungal blood cultures remained negative for the patient, including a sample taken prior to IV antifungal treatment. This surprised the treating team, as the PET scan showed multiple sites of reactive changes in bone marrow, indicative of hematogenous spread of the *Candida parapsilosis*. This is readily explained if the initial culture was a false negative, and subsequent cultures were appropriately treated. If only a single culture is taken, *Candida* species have a sensitivity ranging between 60–75% [14]. This increases to 95–100% if three cultures are taken. A false negative result may have been avoided had the treating team collected more samples prior to IV antifungal therapy. Nevertheless, the BM aspirate culture provided diagnosis and guided therapy, and the blood culture result had no bearing on treatment.

BM *Candida* in immunocompetent individuals is rare but has been reported once in medical literature. Zimpfer et al. describes the case of an immunocompetent patient with BM trephine biopsy showing budding yeast and pseudohyphae within the interstitium of the sample. As the sample was fixed in formalin, it was unable to be submitted for culture. Staining tests indicated that the microorganisms were of *Candida* species. Furthermore, serum testing showed the patient had raised anti-*Candida albicans* IgG and IgM antibodies, indicating that this was the causal agent [5]. Our case is unique in comparison for three important reasons; firstly, the detection of PET-avidity within our patient's BM was a useful tool for guiding the ultimate diagnosis. Secondly, *Candida parapsilosis* was specifically found through the use of an aspirate culture. Thirdly, our trephine histopathology did not show any of the same findings as Zimpfer's case. BM culture and histopathology can independently lead to a diagnosis, as evidenced in these two cases.

There are also cases of *Candida parapsilosis* osteomyelitis in the literature [15,16], however these are all associated with penetrating trauma, IV drug use, or surgery (typically orthopedic), none of which our patient had prior to admission. Furthermore, these patients presented with focal areas of infection, which facilitated faster diagnosis, whereas our patient had systemic features of illness with no apparent source, making diagnosis more difficult. Our use of a PET scan to facilitate diagnosis was also unique in comparison to this other case.

Conclusion

This is a case of an invasive fungal infection in an immunocompetent individual whereby a BM aspirate culture provided a definitive diagnosis. While the BMAT was indicated due to systemic illness, PET-avid imaging, and concerns for hematological malignancy, the procedure itself is a highly invasive one that requires careful consideration. While systemic fungal infections are typically associated with immunocompromised patients, a relatively immunocompetent patient may still be infected with an opportunistic pathogen. It is important to consider invasive fungal infections as a differential in patients with an infectious presentation refractory to antibiotics, regardless of immune function status. Additionally, when investigating patients for fevers with a BMAT, we would recommend consideration of an aspirate culture in discussion with hematology and infectious disease teams. While a BM aspirate culture can certainly change management, as evidenced in our case, this is quite a rare occurrence and should not necessarily dictate future patient investigations, as overall yield for the test is low.

CRediT authorship contribution statement

Min-Ne Wu: Supervision, Writing – review & editing. **Aditya Tedjaseputra:** Investigation, Writing – review & editing. **Alistair John Tinson:** Writing – review & editing. **Kirollos Nan:** Writing – review & editing. **Timothy Abrahams:** Writing – review & editing. **Joshua Haron Abasszade:** Supervision, Writing – review & editing. **Paul Bao Duy La:** Supervision, Writing – review & editing. **Nicholas Edwards:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors declare that there are no conflicts of interest in this study. Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

References

[1] Safdar A, Bannister TW, Safdar Z. The predictors of outcome in immunocompetent patients with hematogenous candidiasis. Int J Infect Dis 2004;8(3):180–6.
[2] Trofa D, Gácser A, Nosanchuk JD. *Candida parapsilosis*, an emerging fungal pathogen. Clin Microbiol Rev 2008;21(4):606–25.
[3] Pearson-Stuttard J, Blundell S, Harris T, Cook DG, Critchley J. Diabetes and infection: assessing the association with glycaemic control in population-based studies. Lancet Diabetes Endocrinol 2016;4(2):148–58.
[4] Chapman B, Slavin M, Marriott D, et al., Australian and New Zealand Mycoses Interest Group. Changing epidemiology of candidaemia in Australia. J Antimicrob Chemother 2017;72(4):1103–8.
[5] Zimpfer A, Piehler P, Kofler G, Dirnhofer S, Tzankov A. Isolated bone marrow mycosis in a patient presenting with consumptive symptoms. J Clin Pathol 2004;57(1):107–8.
[6] Mor A, Dekkers OM, Nielsen JS, Beck-Nielsen H, Sørensen HT, Thomsen RW. Impact of glycemic control on risk of infections in patients with type 2 diabetes: a population-based cohort study. Am J Epidemiol 2017;186(2):227–36.
[7] Davis KL, Wei W, Meyers JL, Kilpatrick BS, Pandya N. Association between different hemoglobin A1c levels and clinical outcomes among elderly nursing home residents with type 2 diabetes mellitus. J Am Med Dir Assoc 2014;15(10):757–62.
[8] Timsit J, Azoulay E, Schwebel C, et al. Empirical micafungin treatment and survival without invasive fungal infection in adults with ICU-acquired sepsis, *Candida* colonization, and multiple organ failure: the EMPIRICUS randomized clinical trial. JAMA 2016;316(15):1555–64.
[9] Hot A, Jaisson I, Girard C, et al. Yield of bone marrow examination in diagnosing the source of fever of unknown origin. Arch Intern Med 2009;169(21):2018–23.
[10] Martellosio JP, Puyade M, Debiais C, et al. Bone marrow biopsy diagnostic yield in internal medicine. Post Med 2021;133(1):89–95.
[11] Sai SK, Padhi S, Varghese RGB, Kanungo R, Basheer A, Iqbal N. Diagnostic utility of bone marrow examination in evaluation of fever: a descriptive study on 98 immunocompetent adults from a tertiary care institute in south India. Trop Doct 2019;49(2):88–96.
[12] Gupta R, Setia N, Arora P, Singh S, Singh T. Hematological profile in pyrexia of unknown origin: role of bone marrow trephine biopsy vis-à-vis aspiration. Hematology 2008;13(5):307–12.
[13] Wilkins B, Clark D, Bain B. Bone Marrow Pathology. 5th ed. United Kingdom: Wiley; 2019.

[14] Lee A, Mirrett S, Reller LB, Weinstein MP. Detection of bloodstream infections in adults: how many blood cultures are needed? J Clin Microbiol 2007;45(11):3546–8.

[15] Lopez R, Hunter AR, Geoghegan O, Demertzi E. *Candida parapsilosis* osteomyelitis. BMJ Case Rep 2014.

[16] Ranjit E, Roxborough J, Davis D, Sapra A, Bhandari P. Clavicular osteomyelitis secondary to *Candida parapsilosis* infection. Cureus 2020;12(6):e8699.