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The role of 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (FDG PET/CT) in assessment of complex invasive fungal disease and opportunistic co-infections in patients with acute leukaemia prior to allogeneic haematopoietic cell transplant

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RUNNING HEAD

FDG-PET/CT in invasive infection

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ABSTRACT:

Introduction: Individuals diagnosed with acute lymphoid and myeloid malignancies are at significant risk of invasive fungal and bacterial infections secondary to their marked immunocompromised states with a significant high risk of mortality. The role of metabolic imaging with 18F-Fluorodeoxyglucose (FDG) Positron Emission Tomography/Computed Tomography (PET/CT) has been increasingly recognised in optimising the diagnosis of invasive infection, monitoring the response to therapy and guiding the duration of antimicrobial therapy or need to escalate to surgical intervention.

Methods: Two distinct cases of pulmonary co-infection of rare fungal and bacterial pathogens are explored in severely immunocompromised individuals where FDG PET/CT aided both patients to make a full recovery and transition to HCT. The first case explores mixed Scedosporium apiospermum and Rhizomucor pulmonary infection on a background of T cell/myeloid mixed phenotype acute leukaemia ultimately warranting long term antifungal therapy and lobectomy prior to HCT. The second case explores Fusarium and Nocardia pulmonary infection on a background of relapsed AML also warranting surgical resection with lobectomy and long-term antimicrobials prior to transition to HCT.

Discussion: The cases highlight the utility of FDG PET/CT to support the diagnosis of infections, including the presence or absence of disseminated infection, and to provide highly sensitive monitoring of the infection over time. FDG PET/CT played a key role in directing therapy duration decisions and prompted the necessity for surgical intervention.

Ultimately, the use of FDG PET/CT allowed for a successful transition to HCT highlighting its value in this clinical setting.

Conclusion: FDG PET/CT has an emerging role in the diagnostic and monitoring pathway for complex infections in high risk immunocompromised patients.

KEYWORDS:
FDG PET/CT, invasive fungal infection, opportunistic infection, mucormycosis, Scedosporium, Fusarium, Nocardia, haematopoietic cell transplant.

MAIN TEXT:

1| INTRODUCTION

Individuals diagnosed with acute lymphoid and myeloid malignancies are at significant risk of invasive fungal and bacterial infections secondary to their marked immunocompromised

states. These invasive infections are associated with difficult diagnostic challenges, frequently resulting in poor recovery with a significantly high risk of mortality [1]. The treatment pathway for these patients may include allogenic haematopoietic cell transplantation (HCT) with curative intent. Moreover, invasive fungal infections prior to allogeneic transplant are associated with worse progression free survival and overall survival, although not a contraindication in themselves [2].

We explore two distinct cases of pulmonary co-infection of rare fungal and bacterial pathogens in severely immunocompromised individuals where the application of metabolic imaging using 18F-Fluorodeoxyglucose (FDG) Positron Emission Tomography/Computed Tomography (PET/CT) aided both patients to make a full recovery and transition to HCT. Both cases were managed with long-term antimicrobials and surgery with pulmonary resection. These cases highlight the utility of FDG PET/CT imaging in optimising the diagnosis of complex invasive fungal disease (IFD) in patients with acute leukaemia, as well as monitoring the response to treatments for IFD allowing the transition to HCT– these roles are becoming increasingly recognised in the literature [3-5].

2.1| Case 1: Concurrent pulmonary Scedosporiosis and Mucormycosis prior to HCT

A 51-year-old man who presented with mixed *Scedosporium apiospermum* and *Rhizomucor* sp. invasive pulmonary infection requiring surgical resection and long-term use of liposomal amphotericin B, voriconazole and terbinafine in the context of a newly diagnosed T cell/myeloid mixed phenotype acute leukaemia (T/M-MPAL).

The patient was Ethiopian born and lived in Kenya 2 years prior to migrating to Australia at age 24. He had no previous healthcare work or exposure. His travel history included time back in Ethiopia in the weeks prior to his haematological diagnosis. There were no known exposures to TB.

The diagnosis of T/M-MPAL (normal cytogenetics, FLT3-ITD mutation +, NPM1 mutation -, hypercellular marrow 86.3% blasts) was made in February 2019 when presenting with constitutional symptoms. Staging CT imaging revealed extensive cervical lymphadenopathy

with a single left lower lobe pulmonary nodule measuring 1.0cm. Induction therapy included hyper-fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (Hyper-CVAD). Midostaurin was added on detection of a FLT3-ITD mutation. He had mould prophylaxis with liposomal amphotericin B (100mg IV 3 times a week) due to potential drug interactions between azoles and vincristine or midostaurin, Pneumocystis jiroveci Pneumonia (PJP) prophylaxis with trimethoprim/sulfamethoxazole, and HSV prophylaxis with valaciclovir.

Cycle 1 commenced at week 2 from diagnosis of T/M-MPAL, was complicated with febrile neutropenia and disseminated intravascular coagulation (DIC). CT chest imaging at week 4 from diagnosis of leukaemia revealed new ground-glass bilateral pulmonary nodules, measuring 1.5cm in right upper lobe, 0.9cm in right lower lobe and 2.4cm in left lower lobe. Pulmonary biopsy of right upper lobe nodule revealed pauci-septate hyphae with right angle branching suggestive of angioinvasive mucormycosis and pan fungal polymerase chain reaction (PCR) consistent with Rhizomucor with no growth on cultures. Therapeutic liposomal amphotericin B 400mg IV daily (5mg/kg) was commenced with concurrent empiric antimicrobials. At this stage repeat bone marrow biopsy revealed complete remission with intention to transition to HCT.

At week 5 from diagnosis of leukaemia interval imaging, in the context of further clinical deterioration and to exclude occult disease, via FDG PET/CT (Figure 1.1) revealed increased nodularity size which prompted a video-assisted thoracoscopic surgery (VATS) at week 7 with wedge resection of the right upper lobe and left lower lobe. The right lower lobe nodule was unable to be accessed. Histology was consistent with angioinvasive mucormycosis with fungal elements detected on Gomori and Periodic Acid-Schiff (PAS) stain. Interestingly, fungal culture of the right upper lobe revealed *Scedosporium apiospermum* (susceptible to voriconazole and posaconazole but resistant to amphotericin). By week 8 voriconazole 200mg PO BD in combination to terbinafine 250mg PO BD were commenced in addition to the amphotericin.

Given the high risk of fungal relapse with unexpected and untreated *S. apiospermum* infection, HCT was postponed with a plan to continue triple antifungal therapy guided by close image monitoring with consecutive FDG PET/CT imaging to monitor metabolic and radiologic

improvement. FDG PET/CT imaging performed at week 8 revealed persistent and progressive pulmonary infiltrative changes (Figure 1.2). At week 12 repeat FDG PET/CT revealed marked reduction in pulmonary infiltrates however revealed a new avid para-tracheal lymph node (Figure 1.3). This para-tracheal lesion was monitored with a repeat FDG PET/CT at week 19 identifying increased avidity with an SUVmax 7 (Figure 1.4). This prompted endobronchial ultrasound (EBUS) with biopsy revealing negative cultures but pan fungal PCR positivity for Penicillium spp. The decision was made to continue triple antifungal therapy until the peri-transplant period. At this stage isoniazid was also commenced for a newly positive QuantiFERON, with the presumption initially that this avid node may have represented latent tuberculosis.

Repeat FDG PET/CT at week 31 and 35 post initial diagnosis revealed stable infection with no pulmonary changes and resolution of the avid para-tracheal lymph node. The patient underwent 4 cycles of low dose cytarabine and midostaurin as bridge to transplant with fludarabine/ cyclophosphamide/ total body irradiation (Flu/Cy/TBI) conditioned haploidentical HCT, which was conducted week 42 from initial diagnosis, covered by mould prophylaxis with posaconazole 300mg daily, with therapeutic levels.

The HCT was uncomplicated with neutrophil engraftment day 16 post-transplant and graft versus host disease (GVHD) prophylaxis maintained with tacrolimus until day 126. Posaconazole was also ceased at this time. There was no clinical suggestion of relapsed IFD or tuberculosis and the patient remain in complete remission 8 months post-transplant.

2.2| Case 2: Concurrent pulmonary Fusarium and Nocardia prior to HCT

A 61-year-old Australian born female who presented with pulmonary co-infection of *Fusarium sp* and *Nocardia novis* in the context of relapsed AML on treatment with bi-specific T cell engager (BiTE) therapy after multiple lines of previous therapies.

The patient's history was significant for bronchiectasis with known *Pseudomonas aeruginosa* colonisation, mild chronic obstructive pulmonary disease and an ex-smoker. Her AML (normal karyotype: FLT3 mutation -, IDH2 mutation +) was diagnosed in early 2018 and initially with

cytarabine and idarubicin induction and consolidation. The patient was not deemed to be suitable for HCT when first complete remission (CR1) was met due to the high predicted transplant related morbidity form the pulmonary comorbidities. As she remained minimal residual disease (MRD) positive the IDH2 inhibitor enasidentib was commenced. The AML relapsed 7 months later and re-induction with fludarabine, cytarabine and filgrastim (FLAG) chemotherapy was commenced to which the disease was refractory. Therefore, the patient was enrolled on a FLT3 BiTE clinical trial with an intention to consolidate with an allogeneic HCT if remission was achieved. Antimicrobial prophylaxis with trimethoprim/sulfamethoxazole 160/800mg BD, valaciclovir 500mg daily and posaconazole 300mg daily was continued throughout each line of therapy.

She experienced cytokine release syndrome (CRS) and febrile neutropaenia after BiTE treatment warranting intensive care admission for inotropic support and tocilizumab. Respiratory symptoms including productive cough were present with and initial chest X-ray imaging showed right lower lobe consolidation followed by CT imaging revealing a 69x25mm opacity with ground glass changes. She was empirically managed with cefepime in the setting of a penicillin allergy history but transitioned successfully to oral amoxicillin/clavulanic acid 875/125mg BD for a total of 10 days.

A persistent cough in the absence of fever after this course of antibiotics prompted repeat CT imaging that demonstrated extension of consolidative and ground glass changes to the right upper and lower lobe (Figure 2.1). On week 4 from commencing BiTE therapy, bronchoscopy with bronchoalveolar lavage (BAL) revealed a positive PCR for *Fusarium* sp. with negative galactomannan, bacterial and fungal cultures. PCR was performed at ICPMR Fungal Reference Laboratory, Westmead Hospital, NSW [6]. The patient's initial FDG PET/CT intended to investigate for disseminated fungal infection in the context of persisting pyrexia, imaging revealed extensive and intense uptake in the right lung with SUVmax 9.0 and no dissemination.

Liposomal amphotericin B 300mg daily (5mg/kg) was administered for 4 weeks with an oral switch to posaconazole 300mg daily. However, despite therapeutic posaconazole levels, her respiratory symptoms worsened. At 12 weeks from initiation BiTE therapy, and 8 weeks of

antifungal therapy for Fusarium infection, repeat CT imaging revealed progressive respiratory disease now involving the left upper and lower lobe (Figure 2.2). This prompted escalation to IV cefepime and liposomal amphotericin B whilst a decision was made to progress to surgical intervention with right upper lobe lobectomy. Interestingly, histology did not demonstrate any evidence of IFD, but organising pneumonia which was managed with prednisolone 25mg for 10 days, cessation of cefepime and recommencement of posaconazole.

The patient's respiratory symptoms continued to progress despite surgical intervention and corticosteroids. At week 20 from initiation BiTE therapy, respiratory swab PCR returned positive for Parainfluenzae virus with repeat FDG PET/CT imaging that revealed new bilateral ground glass changes with marked avidity in bilateral fields. Further progressive pulmonary changes at week 22 on CT imaging prompted a repeat bronchoscopy, which interestingly identified *Nocardia nova* on culture of bronchial washings from the right middle and lower lobe (sensitive to amikacin, clarithromycin and linezolid with resistance to ciprofloxacin, doxycycline and imipenem). CT imaging of the brain excluded disseminated disease. The patient was treated with a 4-week course of oral linezolid (600mg) and clarithromycin (500mg) each twice daily and de-escalated to clarithromycin to continue throughout to HCT. CT chest imaging 2 weeks into this treatment revealed marked radiographic improvement.

The patient transitioned to an uncomplicated sibling matched fludarabine and low dose cyclophosphamide conditioned allogeneic HCT at 30 weeks from initiation of BiTE therapy with posaconazole 300mg daily for mould prophylaxis, valaciclovir 500mg daily for HSV prophylaxis and pentamidine 300mg nebulised monthly for PJP prophylaxis. Neutrophil engraftment occurred at day 22 post-transplant, GVHD prophylaxis with cyclosporine was continues until day 90 post-transplant. A decision was made to continue clarithromycin for 6 months post-transplant to reduce risk relapse of Nocardia infection. A follow up FDG PET/CT on day 71 post HCT demonstrated complete pulmonary recovery. A summary of FDG PET/CT imaging for case 2 is provided in Figure 2.3.

A timeline of events in both cases are summarised in Figure 3.1 and 3.2.

3| DISCUSSION

As invasive fungal and bacterial infections are increasingly recognised amongst the haematological population, early diagnostics are imperative to aid focused management, reduce toxicity of empirical therapies, improve outcomes and allow for earlier progression to HCT.

Our two cases highlight the utility of FDG PET/CT to support the diagnosis of infections, including the presence or absence of disseminated infection, and to provide highly sensitive monitoring of the infection over time. In both patients the FDG PET/CT played a key role in directing therapy duration decisions and prompted the necessity for surgical intervention. Ultimately, the use of FDG PET/CT allowed for a successful transition to HCT highlighting its value in this clinical setting.

3.1| The role of FDG-PET/CT

There is an increasingly recognised role for FDG PET/CT in the identification of occult invasive disease, in particular IFD in prolonged neutropenic sepsis, as well as guiding management through monitoring the outcomes of therapy [3-5].

The PET modality functions to identify the uptake of the radiolabelled FDG through cellular metabolism while the low-dose CT is utilised to provide more localised detail of the abnormalities [7, 8]. Maximum standardised uptake value (SUVmax) is generally used to measure the intensity of the FDG uptake at an avid site. Despite its widespread use in clinical practice, this number has little value in distinguishing uptake secondary to an infective or inflammatory aetiology from a malignant lesion and is also subject to technical variations, lesion size and FDG uptake time [9, 10]. Nevertheless, the ranges of SUVmax amongst bacterial and fungal pathogens has been reported throughout multiple studies which can be useful in guiding diagnosis and monitoring therapy [3, 4]. For instance, pulmonary IFD, typically presents with lesions with SUVmax >2.5, which is also the lower range of spectrum amongst low grade and less proliferative malignant lesions [4]. In the majority of these cases however, visual analysis of the uptake pattern combined with clinical presentation and other radiological findings can assist distinction between IFD and a malignant lesion. However, the

confirmatory diagnosis through tissue biopsy is ultimately required to accurately diagnose the type of infection and tailor antibacterial or antifungal treatment.

In response to an appropriate management, the metabolic intensity of avid infective or inflammatory intra-parenchymal pulmonary changes will decrease over time; however, malignant lesions have been shown to continue to increase in avidity in the absence of active oncological therapy [11, 12]. Though this can differentiate resolving infection from worsening malignancy, this does not remove requirement for a tissue diagnosis.

Amongst patients with leukaemia, clinical and radiological features of invasive infection may be nonspecific and insensitive and contribute to diagnostic difficulty [13]. In this setting a promising role for FDG PET/CT continues to be described in the initial work up of febrile neutropenia in immunocompromised individuals to guide diagnosis, monitor effect of therapy and recognise early signs of disease relapse [4]. In multiple studies, the sensitivity of FDG PET/CT to identify the aetiology of neutropenic sepsis is between 80-93%, markedly higher when compared to high resolution CT with a sensitivity of 53% [14-17]. This has utility in further guiding targeted diagnostic tests and can ultimately hasten the initiation of directed therapy and hence recovery.

High resolution CT is sub-optimal in the diagnosis of IFD due to low sensitivity, often reporting nonspecific pulmonary changes.[15] FDG-PET/CT plays a complementary role by not only confirming the metabolic activity of those changes but also identifying the area of highest metabolic activity which can significantly reduce the likelihood of unsuccessful invasive diagnostic procedures.[4] Whole body functional imaging with FDG-PET/CT enables clinicians to identify not only localised infection but also the extent of disease, potentially identifying further sites of occult infection, dissemination or alternate pathologies.[3, 17] The high negative predictive value for FDG-PET/CT to identify IFD can be utilised to encourage therapy discontinuation in the setting of ruling out invasive infection.[3] Alternatively, this monitoring of disease response can have a role in escalating to surgical therapy in the instance of a lack of treatment response.

In these patients, the FDG PET/CT scans were performed on hybrid PET/CT scanners including GE Discovery (GE Medical Systems, Milwaukee, WI, USA) or Biograph 16 (Siemens Medical Solutions, Erlangen, Germany). Patients were injected with approximately 3.8 MBq/kg of FDG and imaging was performed after 65 (+/-10) minutes. PET/CT scanners at Peter MacCallum Cancer Centre are cross calibrated regularly. Dual time point imaging, in which a second delayed acquisition is obtained, was not employed due to the lack of literature support in this context[18]. In addition, the combination of pattern of FDG uptake, CT changes and clinical information available made the diagnosis of infection far more likely than malignancy.

3.2| Challenges of diagnosing emerging fungal and bacterial pathogens

Patients with acute leukaemia are at high risk for opportunistic infection. While invasive aspergillosis has been the most common invasive fungal infection, rates of non-aspergillus moulds such as Scedosporium and Fusarium, and mucormycosis are becoming increasing identified amongst immunocompromised hosts including the HCT cohort[19, 20]– cases of co-infection of these rarer pathogens are less commonly identified. Furthermore, the incidence of invasive aspergillosis continues to decline due to changed transplantation practices including mould active antifungal prophylaxis as well as nonmyeloablative conditioning and prompt diagnostics.[21, 22] These implicated organisms in our cases have high mortality rates hence emphasizing the importance of early pathogen detection and management.

3.3| Management challenges of invasive fungal and bacterial pathogens

Management of rare invasive fungal and bacterial infections is challenging. Difficulties arise due to the variable intrinsic resistances of these organisms, high rates of mortality and challenges in monitoring disease response. These challenges often delay or even prevent the transition to HCT in patients with acute leukaemia and invasive infection. The role for FDG-PET/CT, which provides imaging as well as a measure of infection activity, can aid these complex management challenges.

Specific to our cases, guidance to the management of co-infection is further limited due to a paucity of data amongst the literature. Three case reports exist of Mucormycosis and Scedosporium co-infections, however these all represent multisystem or disseminated disease [23-25]. No documented *Fusarium* and *Nocardia* single organ co-infections were identified in the literature.

Recommended antifungal management guidelines for each pathogen is summarised, the key challenge pertains to an unclear duration of antifungal courses.[26-29] Current strategies utilise the treating clinician's acumen to identify symptoms clearance or radiographic improvements to drive therapy cessation.

Scedosporium infections have limited treatment options and usually commence with voriconazole (+/- terbinafine) therapy.[30, 31] Initial therapy of mucormycosis is usually liposomal amphotericin B although there are species with varying azole resistances.[28, 32] *Fusarium* sp. has variable susceptibility amongst these antifungal agents.[33] These varying antifungal therapies, due to resistance patterns, highlight the importance for a prompt and accurate diagnosis of fungal infection and their susceptibility profile to guide treatment decisions.

Management guidelines for Nocardia have more clarity than IFD. First line therapy utilises trimethoprim/sulfamethoxazole with alternate options including third generation cephalosporins, imipenem or amikacin. In disseminated disease therapy duration is recommended beyond 12 months followed by an indefinite secondary prophylaxis course.[34]

Surgical excision in pulmonary invasive disease via total or partial lobectomy is well recognised for its role to reduce pathogen burden in bulky disease or in disease refractory to antimicrobials.[35-38] However, disseminated disease or multi-lobar involvement may preclude surgical management.[39] Surgical excision as a bridge to HCT has been utilised.[40] FDG PET/CT has an emerging role in guiding the transition to resection – as identified in both cases.

3.4| FDG PET/CT in guiding the duration of antimicrobial therapy

Guidelines towards the duration of antimicrobial therapy remain unclear for rare invasive infections. The functional capacity of FDG PET/CT to provide information regarding metabolic activity of an anatomical abnormality is utilised to differentiate between changes of active infection from residual chronic inflammation or scar tissue. This distinction can guide therapy duration in the management of IFD or bacterial infection.[4, 41]

The metabolic activity of the lesions on FDG PET/CT was utilised to guide antimicrobial decision making. This was emphasised in case one, where appropriate triple antifungal therapy was continued for a 27-week (7 month) period from the identification of pulmonary co-infection to the timing of HCT. A similar trajectory occurred in case two, where ongoing avidity continued to prompt the use of antimicrobial therapy and then surgical therapy. Relative stability of anatomical changes on CT in these patients at those different time points would have not made treatment individualisation possible in these complex cases.

In these cases, evidence of metabolic resolution via FDG PET/CT was identified through decreasing SUVmax in initially avid lesions over interval imaging in response to antimicrobial therapy or surgical intervention. In both cases, resolving avidity of these pulmonary lesions supported the decision to proceed to HCT.

The role for FDG PET/CT to guide management through interval imaging monitoring disease response drives the clinician's decision towards duration of antimicrobial therapy and supports transition to HCT. On the contrary, images failing to demonstrate an appropriate response to therapy can be utilised to extend antimicrobial use or instead to guide transition to surgical intervention. There is often a significant lag between resolution of infection and clearing of the anatomical changes on CT which would render this modality useless for this purpose in complex patients in whom rapid transition from one treatment modality to another is vital.

3.5| FDG PET/CT in guiding invasive procedures

Whilst FDG PET/CT is utilised for its role to monitor disease response to antimicrobials using interval scanning, failure of a sufficient response can guide decision making surrounding surgical intervention. Localised disease refractory to antimicrobial therapy may be amendable to debulking surgery to gain source control, acting as definitive therapy. Surgical debridement has previously been utilised to hasten infection clearance and support transition to HCT.

In case one FDG PET/CT imaging prompted progression to lobectomy due to minimal response of directed therapy to mucormycosis pulmonary infection. This surgical intervention led to the subsequent diagnosis of *Scedosporium* through newly attained tissue. Of note, FDG PET/CT provides a greater assessment of altered pulmonary architecture in the post-operative setting when compared to conventional CT imaging[4]. Thus, in this case new lymphadenopathy highlighted in interval imaging prompted further targeted diagnostics with EBUS and biopsy to exclude tuberculosis and identify *Penicillium* spp. infection.

In case two FGD PET/CT highlighted inadequate treatment response despite directed antifungal therapy to Fusarium pulmonary infection. This prompted escalation to lobectomy to aid definitive management. Post-operative FDG PET/CT suggested worsening pulmonary changes prompting targeted investigation with bronchoscopy and BAL, providing a diagnosis of Nocardia.

In our cases interval imaging drove action to definitive source control via lobectomy and also guided targeted investigation to further identify causative pathogens. This utility is pivotal in aiding difficult management decisions in rare invasive infection, especially when persistent infection delays transition to HCT.

3.6| Limitations of FDG PET/CT

There remain concerns that FDG PET/CT predisposes to higher levels of radiation when compared to conventional high-resolution CT imaging - the effective radiation dose of whole body FDG PET/CT is reported to be 15mSv, compared to 7mSv for high resolution chest CT or 10mSv for abdomen and pelvis CT[42]. This can be reduced further through using per/kg doses of FDG rather than fixed doses or through reducing the tube-current-time product (mA)

on CT [43]. However, the greater capacity of FDG PET/CT to identify infection earlier, discovering or excluding additional sites of infection outside thorax, identifying an unsuccessful treatment to enable timely switch to another treatment modality and allowing confident discontinuation of an effective treatment to transition to the next treatment line - as all highlighted in our cases - would ideally prevent the need for subsequent diagnostic imaging and reducing cumulative exposure to radiation. Though the image resolution on low dose CT component of the PET is not as high as high-resolution CT, this is arguably sufficient enough to obviate the need for subsequent diagnostic CTs to monitor therapy after the baseline scan.

At this stage the greatest limitations of FDG PET/CT pertain to issues of rather limited Medicare accepted indications, generalised access and affordability [3, 5]. The utility of FDG PET/CT imaging in guiding diagnostic and management protocol requires ongoing assessment, promotion and education to enhance distribution and access. This case series highlights how careful patient selection could assist treatment individualisation in the era of precision medicine beyond oncology FDG PET/CT.

The future of molecular imaging remains promising, with further areas of discovery pertaining to the use of immune-PET/MR which utilises the role of specific antibodies to specific infections, such as Aspergillosis, identify pathogens and extent of disease processes [44].

4| CONCLUSIONS

These complex cases highlight the utility of FDG PET/CT in the diagnostic and management approach to occult invasive fungal and bacterial infection with the ultimate transition to successful potentially curative HCT. Both cases highlight rare invasive pulmonary co-infection amongst immunocompromised hosts with haematological malignancies. Both cases utilised FDG PET/CT for its emerging role in identification and location of disease, excluding additional sites of infection prior to surgery and monitoring response to antimicrobial treatment and disease progression. Subsequent planning of management options such as site of surgical resection was guided by interval FDG PET/CT imaging. Post-operatively, FDG PET/CT was

further utilised to monitor recovery and provided information about infection response and when to proceed to HCT.

The role of FDG PET/CT in infection continues to be established, in these cases we have highlighted a very clear role in diagnostics and aiding successful management of invasive fungal and bacterial infection. We suggest further prospective controlled studies that support the widespread adoption of FDG PET/CT are necessary, as associated radiation exposures, costs and the follow up of positive lesions with invasive testing are not insignificant.

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CONFLICTS OF INTEREST

There are no conflicts of interest

AUTHOR CONTRIBUTIONS

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Analysis and interpretation of data: Anthony Longhitano

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CRediT STATEMENT

Anthony Longhitano: study design, writing – original draft, writing – review and editing. **Ramin Alipour**: writing – review and editing. **Amit Khot**: writing – review and editing. **Ashish Bajel**: writing – review and editing. **Phillip Antippa**: writing – review and editing. **Monica Slavin**: study design, supervision, writing – review and editing. **Karin Thursky**: study design, supervision, writing – review and editing**.**

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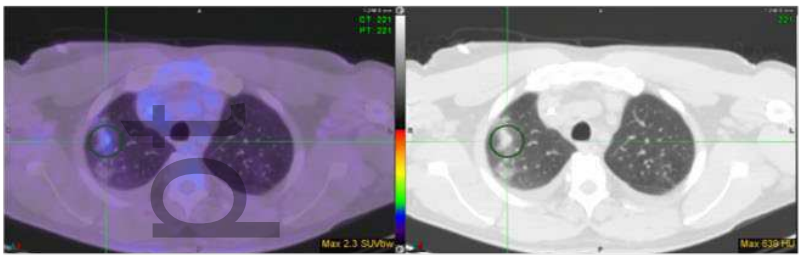

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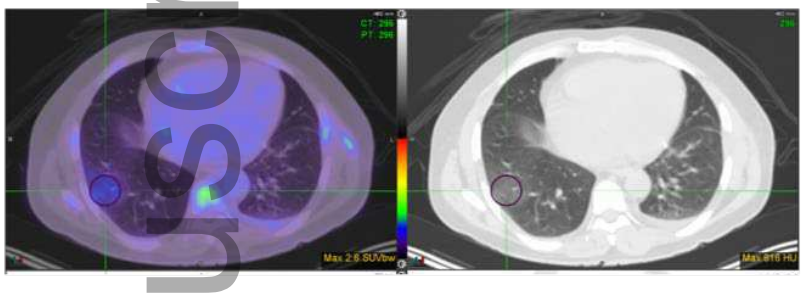

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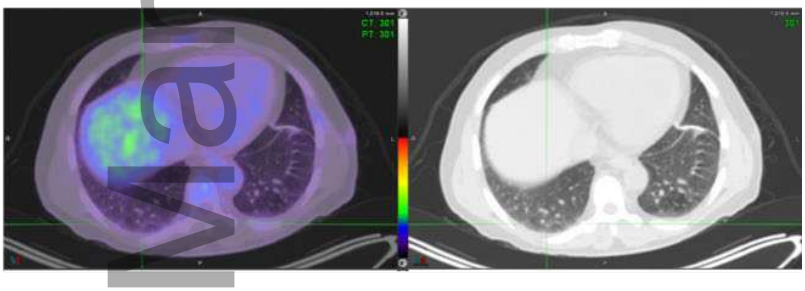

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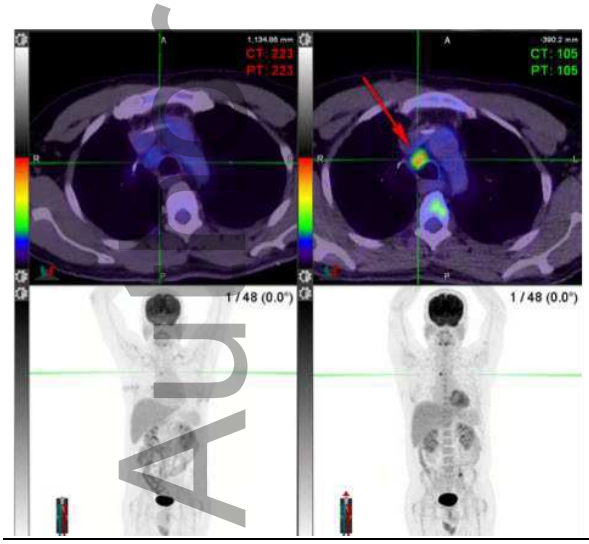

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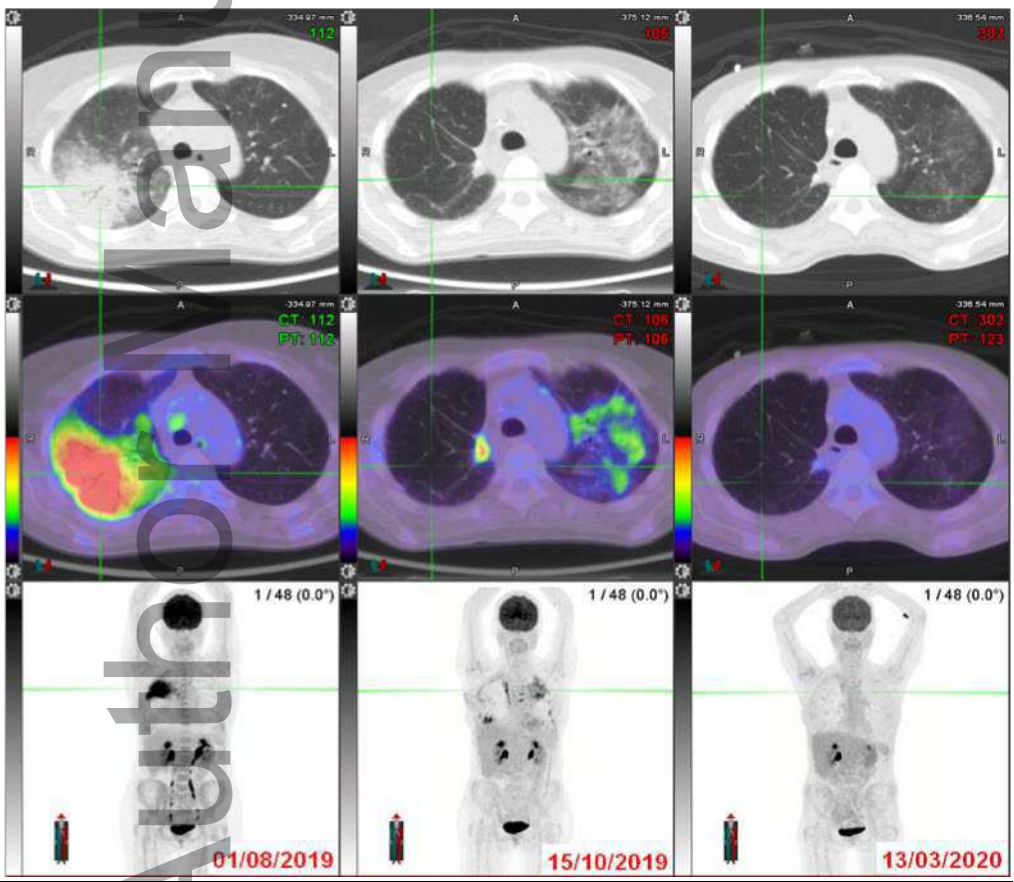

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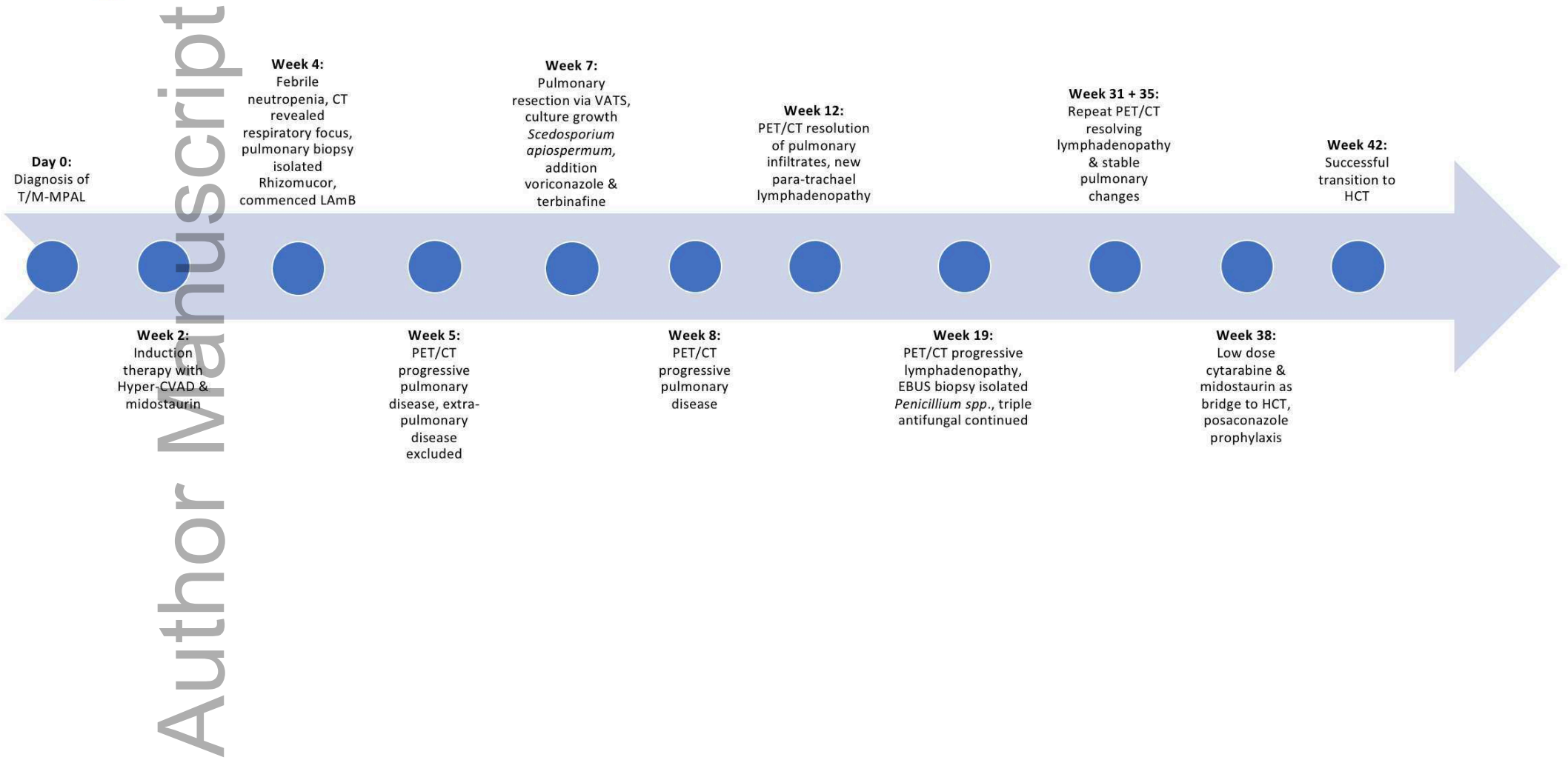

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