

# Recurrent opportunistic infections in a post-transplant lymphoma patient

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## ABSTRACT

**Introduction:** Infections and graft-versus-host disease (GVHD) are the most notable problems after allogeneic stem cell transplantation (Allo SCT). **Case Report:** A 50-year-old patient underwent an Allo SCT for transformed follicular lymphoma (t-FL). Transplant course of the patient was complicated by GVHD and recurrent, severe, opportunistic infections including pneumonia caused by two fungal pathogens simultaneously, recurrent bacteremia with no apparent source, septic arthritis caused by an unusual pathogen and eventually developed progressive multifocal leukoencephalopathy (PML). **Conclusion:** This case illustrates the diversity of opportunistic infections affecting patients undergoing Allo SCT and the complexity involved in diagnosis and treatment of such infections.

**Keywords:** Allo SCT, GVHD, Opportunistic infections, Follicular lymphoma (FL), PML

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## INTRODUCTION

Infections and graft-versus-host disease (GVHD) are the most notable problems after allogeneic stem cell transplantation (Allo SCT).

We describe a 50-year-old patient who underwent an Allo SCT for transformed follicular lymphoma (t-FL) and whose transplant course was complicated by GVHD and recurrent, severe, opportunistic infections including pneumonia caused by two fungal pathogens simultaneously, recurrent bacteremia with no apparent source, septic arthritis caused by an unusual pathogen and eventually developed progressive multifocal leukoencephalopathy (PML).

## CASE REPORT

A 50-year-old male patient was diagnosed with t-FL and underwent an Allo SCT from matched sibling donor without T-cell depletion, resulting in durable complete remission. His posttransplantation course was initially complicated by an early onset of acute GVHD, grade III, with gastrointestinal (GI) and hepatic manifestations including diarrhea and deranged liver function tests (LFTs) including increased bilirubin which were successfully controlled with prednisone and cyclosporine. Prednisone was given at a dosage of 80 mg for several weeks.

One month later, the patient was hospitalized with high fever, general weakness, dry cough and dyspnea. At the time of admission, his vital signs were stable. Blood pressure was 125/70 mmHg and pulse was 86 bpm. Initial laboratory investigations including liver function tests were within normal range apart from macrocytic anemia hemoglobin (Hb) 9.5 g/dL and mild thrombocytopenia  $7.2 \times 10^5/\text{mm}^3$  with a normal neutrophil count. A chest X-ray (CXR) revealed bilateral lung infiltrates. On a chest computed tomography (CT) scan multiple nodular lesions with halo sign were noted. Urine Legionella antigen was positive and culture of bronchoalveolar lavage (BAL) fluid grew Legionella species. Aspergillus DNA and Legionella DNA were detected in BAL fluid using polymerase chain reaction (PCR) and Galactomannan was negative, establishing the diagnosis of simultaneous Legionella pneumonia and invasive pulmonary aspergillosis (IPA). The patient was treated with voriconazole and levofloxacin and showed clinical improvement. The patient was on weekly follow-up with the hematology clinic and his condition was stable.

Three months Allo SCT, a multidrug-resistant Aspergillus Campylobacter jejuni was isolated from blood cultures drawn from a central venous catheter (CVC) and from peripheral blood as well as stool culture. The patient was treated with imipenem for two weeks. Extensive search for the source of recurrent bacteremia including venous ultrasound doppler examination and a trans-esophageal ecocardiogram (TEE) was unrevealing.

Concomitantly, the patient became disoriented. Brain CT scan and magnetic resonance imaging (MRI) were within normal limits. Lumbar puncture (LP) was performed, to obtain cerebrospinal fluid (CSF) for culture and molecular studies, for the detection of viral, bacterial and fungal pathogens. A laboratory results for viral, bacterial and fungal studies were negative. The neurologic manifestations were attributed to side effects of imipenem, and treatment was switched to meropenem. The patient gradually regained his previous cognitive status.

One month later, the patient was readmitted due to aggravation of left shoulder pain without fever. Ultrasound, CT and MRI of the shoulder were suspicious for septic arthritis (Figure 1). Arthrocentesis of the shoulder joint effusion revealed purulent fluid with white blood count of  $4.1 \times 10^4/\text{mm}^3$ . Synovial fluid gram stain yielded gram positive bacilli and culture grew Nocardia spp. that were identified as *N. cyrgeorgica* by PCR. Due to trimethoprim/sulfamethoxazole allergy, treatment with imipenem and amikacin was initiated.

Seven months after Allo SCT, the patient developed gait imbalance and delirium. Initial work-up revealed no electrolyte imbalances as well as normal renal function and LFTs. MRI demonstrated a diffuse process involving both frontal lobes (Figure 2). Lumbar Puncture was repeated. The CSF contained leucocytes  $3/\text{mm}^3$ , a normal glucose level, and slightly elevated protein level. Gram stain, CSF culture and cryptococcal antigen test were all negative. PCR of the CSF for

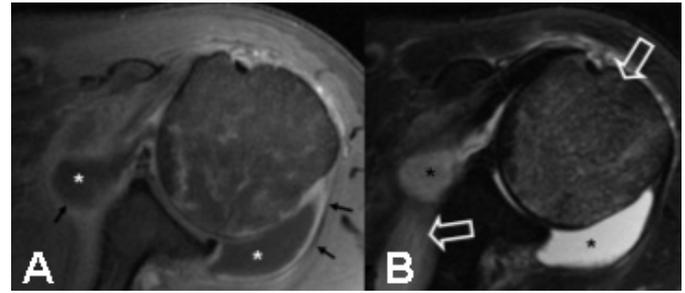


Figure 1: Axial T1 weighted image following gadolinium injection, (A) and axial T2 weighted, (B) MRI of the left shoulder. A large joint effusion (asterisk) with peripheral enhancement (arrow) is noted. Additionally, edema of the humeral head and adjacent soft tissues is shown (B, open arrow).

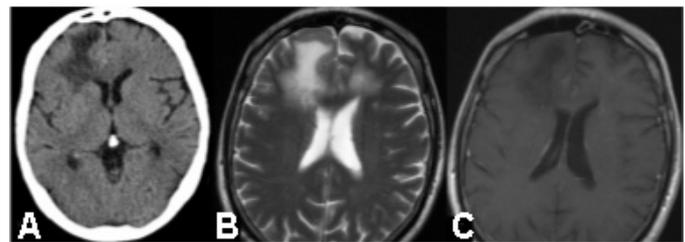


Figure 2: Axial CT, (A), and MRI images of the brain, T2 weighted, (B) and T1 weighted following gadolinium injection, (C). A white matter lesion is noted in the right frontal lobe on CT and bilaterally on MRI, right greater the left. The lesion extends to the subcortical white matter, does not enhance and has a mild mass effect (imaging characteristics typical for progressive multifocal leukoencephalopathy).

Epstein-Barr virus, Cytomegalovirus, Herpes simplex virus, human Herpes virus 6 and Varicella Zoster virus were negative. Serum serology for West Nile virus was negative. PCR for JC virus demonstrated more than a million copies/mL in CSF. An effort to reduce immunosuppression resulted in a flare of the GVHD. Treatment with mefloquine and liposomal cidofovir was initiated but the patient's neurological status continued to deteriorate until his death two weeks later.

## DISCUSSION

Three risk periods of immunologic deficiency occur predictably in recipients of Allo SCT—the pre-engraftment period, the early post-engraftment period (until day 100) and the late period (after day 100).

The late posttransplantation period is heralded by the recovery of cell-mediated immunity (CMI) and humoral immunity. This phase begins at day 100 and continues until the bone marrow transplant (BMT) recipient stops all immunosuppressive medication for GVHD. During this period, viruses are responsible for more than 40%, bacteria for approximately 33% and fungi cause approximately 20% infections [1]. Our patient experienced recurrent infections, including

Legionella pneumonia and pulmonary aspergillosis followed by septic arthritis due to Nocardia and eventually PML caused by JC virus. Among these, IPA exhibits a bimodal distribution, with the first peak at two to three weeks posttransplant and the second peak at three to four months posttransplant, usually in conjunction with persisting GVHD. The remaining pathogens occur primarily in conjunction with immunosuppression connected to treatment of GVHD and appear more remotely after Allo SCT.

The initial CXR and CT in our patient suggested an atypical or opportunistic infection with difficulty in differentiating between IPA and Legionella. Immunosuppression increases the risk for invasive fungal infection and is consistently implicated as a risk factor for Legionella pneumonia with transplantation recipients at the highest risk [2]. Thus the need for BAL testing. Isolation of Legionella in the BAL in conjunction with positive Legionella PCR from BAL and positive urine Legionella Antigen, definitively verified the diagnosis of Legionella pneumonia in our patient.

As stated, the onset of Aspergillus infection after Allo SCT occurs in a bimodal distribution. In a recent epidemiological multi-center survey conducted between 1999 and 2003, aspergillosis was the most frequent fungal complication among patients receiving allogeneic transplant, among whom aspergillosis is responsible for 81% of all fungal infections [3]. The lungs represent the most frequently involved site for invasive aspergillosis and predisposing factors include powerful immunosuppressive chemotherapy, neutropenia and synergistic combinations of potent broad-spectrum antibiotics [4]. In our patient, specific risk factors included Allo BMT, immunosuppressive therapy, GVHD and occasional neutropenia.

As opposed to the diagnosis of Legionella pneumonia our patient did not meet the criteria of proven invasive pulmonary aspergillosis. In the case of suspected IPA, the evaluation should include a radiologic examination of the lungs, sinuses and brain, bronchoscopy and BAL for microscopy, culture and PCR and a test for circulating galactomannan [4]. The definite diagnosis of IPA requires a positive culture or histopathology. Our patient was diagnosed with IPA following a typical chest CT scan and the presence of positive PCR for Aspergillus in BAL, but BAL galactomannan antigen and culture for Aspergillus were notably negative.

The respiratory infection in our patient was followed by persistent Campylobacter bacteremia arising from his gut. Blood stream infection, in general, has been examined primarily in immunocompromised patients with neutropenic fever among whom approximately 50% are ultimately diagnosed with an infectious cause and 20% yield positive blood cultures. Campylobacter bacteremia is a rare disease, occurring mainly in patients with immune deficiency or other serious underlying conditions [5]. In an unpublished study conducted in our institution, Campylobacter bacteremia occurred chiefly among severely immunocompromised patients, especially those with

hematological malignancy. Campylobacter jejuni subsp. Jejuni is the main bacterial cause of enteroinvasive diarrhea, and it is rarely complicated by bacteremia or extraintestinal localization [6].

Shortly after the bacteremia, our patient presented with septic arthritis caused by Nocardia. Immunodeficiency is a well-established risk factor for nocardiosis. Pulmonary disease is the predominant clinical finding of systemic nocardial infection, with the CNS as the second-most involved system in one large survey [7]. Nocardial septic arthritis is significantly less common, and is usually attributed to hematogenous spread in immunocompromised hosts [8]. *N. asteroides* complex is the most common species causing septic arthritis, but *N. braziliensis*, *N. caviae* and *N. farcinica* have also been identified.

The last infectious complication which developed in our patient was PML. As previously described, the patient presented with neurologic, clinical and radiologic findings suggestive of pyogenic brain abscess, which in the immunosuppressed patient has a broad differential diagnosis including viral, bacterial and fungal agents. Amongst these, the most common infectious agents include the herpes virus group and adenovirus, infection with the bacteria *Listeria* and *N. asteroides*, *M. tuberculosis*, *Mucorales* sp, *Candida* and *C. neoformans* [9].

Our patient was diagnosed with PML. This rare and usually fatal viral disease is characterized by progressive damage or inflammation of the white matter of the brain at multiple locations. It occurs almost exclusively in people with severe immune deficiency and is caused by JC virus, which is normally present and kept under control by the immune system. Immunosuppressive drugs prevent the immune system from controlling the virus and reactivation can occur. Symptoms include weakness or paralysis, vision loss, impaired speech and cognitive deterioration.

PML is diagnosed by the finding of JC virus DNA in CSF or brain biopsy. Characteristic evidence of the damage caused by PML in the brain can also be detected on MRI images which classically show multifocal non-enhancing lesions without mass effect.

Currently, there are no approved therapies for PML. Although a number of preclinical reports and case studies have suggested the potential anti-PML effects of antiviral and antineoplastic drugs such as cytarabine, cidofovir and topotecan, larger case-controlled studies failed to establish the efficacies of these medications. In-vitro data coupled with biodistribution data suggest that mefloquine could represent an effective therapeutic agent for the treatment of PML [10]. Accordingly, our patient was treated with the combination of mefloquine and cidofovir.

## CONCLUSION

Our case illustrates that a range of opportunistic infections can affect a patient undergoing Allo SCT during a relatively short period of time. Furthermore,

the appearance of Nocardial infection in the form of septic arthritis is a rare presentation of this pathogen.

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### Author Contributions

Ayelet Raz-Pasteur – Conception and design, Acquisition of data, analysis and interpretation of data, drafting the article, Final approval of the version to be published

Yaakov Dickstein – Conception and design, Acquisition of data, Critical revision of the article, Final approval of the version to be published

Ilana Oren – Conception and design, analysis and interpretation of data, Critical revision of the article, Final approval of the article

Ayelet Eran – Analysis and interpretation of data; Drafting the article; Final approval of the article

Irit Avivi – Analysis and interpretation of data, Drafting the article, Final approval of the article

Khetam Hussein – Analysis and interpretation of data, Drafting the article, Final approval of the article

### Guarantor

The corresponding author is the guarantor of submission.

### Conflict of Interest

Authors declare no conflict of interest.

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