**Fatal mucormycosis and aspergillosis in an atypical host: What do we know about mixed invasive mold infections (MIMI)?**

**Purpose:** Mixed invasive mold infections (MIMI) are rarely diagnosed given lack of non-invasive diagnostic methods with adequate sensitivity. Previous studies, including one case of fatal mucormycosis with positive Aspergillus galactomannan (GM) at our institution, have implied that corticosteroid administration is an important, potentially underestimated risk factor for MIMI. We present a case of fatal MIMI in a host with no classic risk factors for MIMI other than high-dose corticosteroids, and review the literature on MIMI.

**Results:** Autopsy showed 1. filamentous, FITE stain-positive organisms consistent with Nocardia in the brain; 2. multiple septate, narrow-angled hyphae invading the vessels and lung parenchyma. Lung cultures were positive for Aspergillus fumigatus; 3. acute invasive mold infection of the heart, left kidney, thyroid, lymph nodes and brain, with numerous fungal hyphal forms of a second morphology, consistent with Mucor (aseptate, wide-angled), in the parenchyma and blood vessels. Molecular study (28s rRNA) was positive for Lichtheimia corymbifera.

**Case Study:** A non-neutropenic 79-year-old man with history of hypertension and CLL presented with dysphasia after his first cycle of chlorambucil (alkylating agent) and obinutuzumab (CD20-directed cytolytic monoclonal antibody). He had worked for many years in construction and was still very active in his house and garden. Brain MRI showed three distinct abscesses in the left parietal and temporal lobes with significant edema and mass effect, for which he was started on dexamethasone. Chest CT showed one pulmonary nodule. Initial b-D-glucan (bDG) and GM were negative. Stereotactic biopsy of one abscess failed to include its necrotic core and was non-diagnostic.

Cell-free DNA next generation sequencing (cfDNA-NGS) of a plasma sample showed strong signal for Nocardia abscessus, therefore he was started on treatment with intravenous antibiotics. Repeat imaging showed decrease in the size of all brain abscesses and the pulmonary nodule, which demonstrated central cavitation. Brain edema deteriorated upon tapering the corticosteroids, therefore the patient remained on high-dose dexamethasone. Two months after his initial presentation, he presented with multiple new lung abscesses, heart failure and renal failure. Repeat bDG was negative, but GM was >8 (assay cut-off). His family opted for comfort measures only and kindly agreed to an autopsy.


**CONCLUSIONS:**
1. The incidence of MIMI is likely underestimated.
2. High-dose corticosteroid administration is a major risk factor for IMI, including mucormycoses and MIMI.
3. “Immunomodulating” factors, such as immunosenescence and immunosuppression not meeting classic host criteria for IMI (e.g. CLL) may be important contributors.
4. There is an urgent and unmet need for well-designed studies on:
   a) the “net state of immunosuppression” and environmental exposure as risk factors for (M)IMI;
   b) non-invasive fungal diagnostics, including serial cfDNA-NGS and development of new assays;
   c) efficacy, safety and cost-effectiveness of anti-mold prophylaxis in potentially susceptible hosts, other than transplant recipients and neutropenic patients.