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Interesting Images

Candidaemia in an Orthopaedic Patient Detected Coincidentally by Peripheral Blood Smear

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Abstract: An elderly male, with recent COVID-19 and cardiovascular comorbidities, had a prolonged hospitalisation due to periprosthetic joint infection and bacteraemia, post hip hemiarthroplasty. Despite the initial clinical improvement while under targeted antimicrobial therapy, low-grade fever and signs of myelosuppression later occurred. In the May-Grünwald-Giemsa stain of peripheral blood smear (PBS), pseudohyphae among RBCs and phagocytosed blastospores in neutrophils and monocytes were detected, indicating candidaemia and not contamination of the stain. Echinocandin treatment was immediately initiated, and *Candida albicans* was identified, using multiplex PCR, from the obtained blood cultures. Despite the early initiation of antifungal therapy and the removal of the CVL (central venous line), the patient passed away within the next twenty-four hours. Candidaemia is a leading cause of nosocomial bloodstream infections with very high morbidity and mortality and is associated with multiple risk factors (surgery, CVLs, prolonged hospitalization, concomitant bacterial infection, broad-spectrum antibiotics, immunosuppression). The isolation from blood cultures is the gold standard for candidaemia diagnosis. Detection of candidaemia by PBS is extremely rare, requires an experienced microscopist, and is considered to be an emergency. Clinical suspicion, early laboratory identification, and immediate clinician notification can lead to prompt antifungal treatment.

Keywords: candidaemia; bloodstream infection; periprosthetic joint infection; phagocytosed blastospores; pseudohyphae; monocytes; neutrophils; peripheral blood smear; multiplex PCR

Invasive candidiasis comprises both candidaemia and deep-seated tissue candidiasis and typically occurs among hospitalized patients. It has been reported to affect more than 250,000 people worldwide causing more than 50,000 deaths every year. Candidaemia is the most common manifestation of invasive candidiasis and is mentioned in the literature as the fourth most common bloodstream infection and a leading cause of nosocomial bloodstream infections, with very high morbidity and mortality (overall 90-day mortality: 43%) [1,2]. Detection of candidaemia by peripheral blood smear (PBS) is very rare and requires high yeast concentration $\geq 1-5 \times 10^5$ cfu/mL and evaluation by an experienced microscopist [3]. It constitutes an emergency as it shows advanced infection and immediate treatment is required [2]. Finding phagocytosed blastospores in the cytoplasm of leukocytes in addition to free blastospores and pseudohyphae is essential to exclude contamination of the stain and to confirm true candidaemia [4].

Surgical Site Infection (SSI) is one of the major complications following hip or knee insertion, with early onset infection occurring within the first three months after surgery. The incidence of prosthetic joint infection (PJI) following primary total hip arthroplasty (THA) is lower than in knee arthroplasty and is estimated to be approximately 1%. The vast majority of PJI are bacterial, while fungal prosthetic joint infection (fPJI) constitutes about 1-2% of the total PJI and is usually caused by *Candida* spp. A total of 372 fPJI cases have been reported in the literature, with 161 of them being complication of THA [5].



An elderly male, with a history of coronary artery bypass graft (CABG) and hypertension was hospitalized in the Orthopaedic Clinic due to periprosthetic joint infection (PJI) and bacteraemia post hip hemiarthroplasty. The patient was initially admitted for subcapital femoral fracture after fall from standing, while there was also a history of a recent hospitalization due to SARS-CoV-2 infection, treated with remdesivir and dexamethasone. He was discharged postoperatively with instructions for mobilisation and wound cleansing, however, follow-up revealed the presence of periprosthetic infection. Surgical debridement of the arthroplasty, initially performed, failed to control the infection. Finally, the patient underwent removal of the prosthesis (Girdlestone procedure), vac drainage, and placement of a central venous line (CVL), for coverage with targeted antibiotic therapy against pathogens isolated from blood (MRSA) and wound (tissue, pus) cultures (MRSA, *P. aeruginosa*, *P. mirabilis*), while transfusions and fluid/electrolyte replenishment were also needed. The patient initially improved and became hemodynamically stable but gradually the complete blood count (CBC) revealed signs of myelosuppression. Low grade fever reoccurred, and the latest CBC showed severe thrombocytopenia. The urine analysis showed blastospores and a peripheral blood smear (PBS) was prepared to confirm the findings of the CBC. In the May–Grünwald–Giemsa stain (MGG) of PBS pseudohyphae and free blastospores were coincidentally detected (Figure 1).

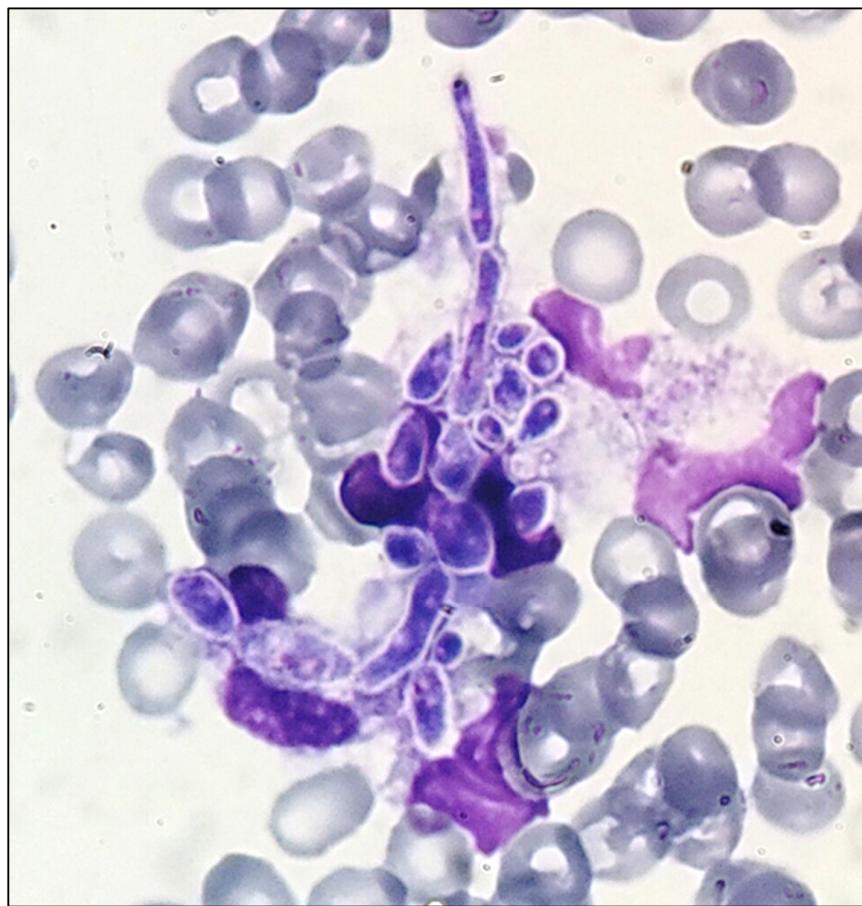


Figure 1. Peripheral blood smear with yeast's blastospores and pseudohyphae among red blood cells [May-Grünwald-Giemsa stain (MGG); original magnification, $\times 1000$].

Further assessment of the smear confirmed our initial findings, as a phagocytosed blastospore was detected in the cytoplasm of a monocyte: the first blastospore that was detected in a WBC (Figure 2).

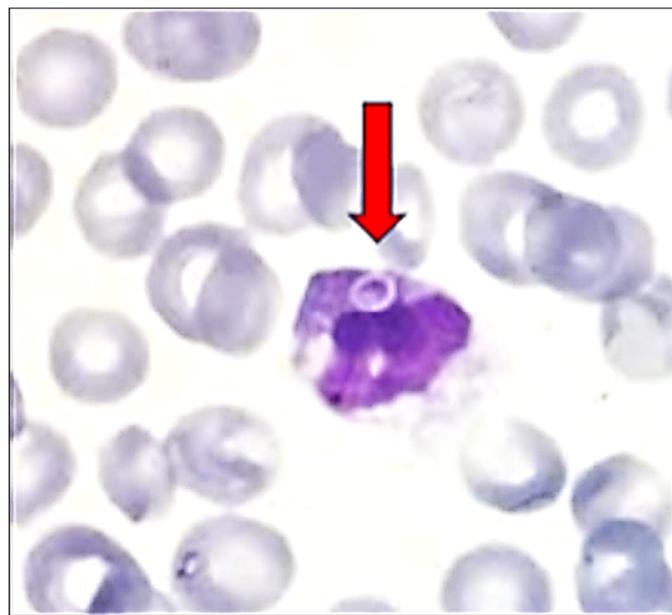


Figure 2. Peripheral blood smear with yeast's blastospores in the cytoplasm of a monocyte: the first blastospore that was detected in a WBC (MGG); (original magnification, $\times 1000$).

Candidaemia is associated with multiple risk factors [6,7]. Communication with the attending orthopaedic surgeon concerning the patient's history raised higher suspicion, as it confirmed the co-existence of many, among them: precedent surgery, CVL and Foley, prolonged hospitalization, concomitant bacterial infection, and broad-spectrum antibiotics. Meticulous examination of the blood smear further revealed: phagocytosed blastospores in both monocytes and neutrophils, as well as another site of free blastospores among red blood cells (Figure 3). An echinocandin was administered, according to the guidelines, as empiric treatment for suspected candidiasis [8,9]. Due to the emergence of non-albicans *Candida* spp. and the coexistence of previous hospitalizations, increasing the risk of possible exposure to *C. auris*, the use of an azole was avoided. Blood cultures were immediately obtained after communication and were urgently processed using Film Array multiplex PCR, identifying *C. albicans*. *Candida* is routinely initially detected in the Gram stain of positive blood cultures, and prompt notification of the clinician is required to start empirical antifungal treatment. Isolation from positive blood cultures remains the gold standard for diagnosing candidaemia [7]. Identification and antifungal susceptibility testing, using Vitek2, showed fluconazole sensitive *C. albicans* in both the urine and the blood culture of the patient. Despite echinocandin administration and CVL removal, the patient passed away within the first 24 hours after the initial diagnosis [10].

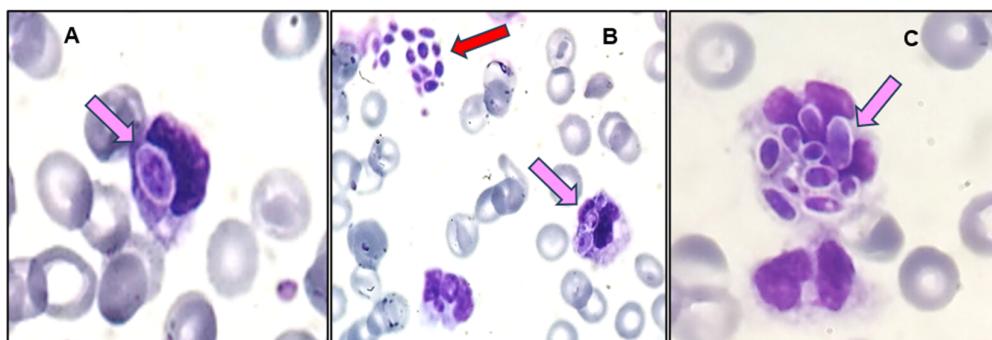


Figure 3. Peripheral blood smear with yeast's blastospores in the cytoplasm of a monocyte (A) and a neutrophil (B, C: pink arrows) and free among RBCs (B: red arrow) (MGG); (original magnification, $\times 1000$).

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