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Case report

Necrotizing fungal gingivitis in a patient with acute myelogenous leukemia: Visible yet obscure

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ABSTRACT

Oral fungal infections present with atypical and varied manifestations, and distinguishing them from other entities including leukemic infiltration can be diagnostically challenging. In this report, we describe a 62 year old female with acute myeloid leukemia who presented, towards the end of her second treatment cycle of decitabine in a prolonged neutropenic state, with a month of painful, necrotic-appearing marginal gingival lesions. She was duly initiated on empiric broad spectrum antifungal treatment but did not show a clinical response with the appearance of new skin lesions concerning for progressive fungemia. Concurrent gingival and cutaneous biopsy showed fungal invasion with *Fusarium*. Despite changing antifungal treatment the lesions progressed, and white blood cell (WBC) transfusions were instituted. The patient had an impressive response with gradual resolution of the skin lesions and regression in gingival lesions over a week of therapy. This case illustrates the highly atypical, confounding appearance of oral fungal infections in immunocompromised hematological malignancy patients. Maxillary and mandibular marginal gingival involvement, although extremely rare, should be recognized as potential sites of fungal involvement. Accurate diagnosis entails a biopsy especially in ambiguous clinical scenarios, as presented here. The role of WBC transfusions in the management of these rare fungal pathogenic infections needs to re-established.

1. Introduction

The incidence of opportunistic invasive fungal infections among the general population has increased significantly over the past two decades [1–3]. This is primarily related to a growing number of at-risk immunocompromised patients with AIDS, advanced malignancies, long-standing diabetes mellitus, and recipients of bone marrow and solid organ transplants, on long-term immunosuppressive therapies [4]. It has long been known that immunosuppression provides a haven for normally avirulent opportunistic pathogens like *Candida*, *Aspergillus*, *Rhizopus* and *Fusarium* to proliferate and disseminate, causing potentially life threatening fungal infections. While the majority of fungal infections continue to be attributed to *Aspergillus* and *Candida*, the pathogenic spectrum is expanding with infections from a variety of rare opportunistic pathogens, especially rare mold species, becoming more common [5,6]. Various factors including more intense immunosuppression with novel agents and steroid-sparing regimens, selective pressures from anti-fungal prophylaxis practices, prolonged survival beyond expectancy of previously fatal diseases and improved laboratory identification techniques, among others have been cited as important factors behind this changing epidemiology [7,8]. While the fluctuating spectrum of fungal pathogens has resulted in a concurrent increase in the development of newer, expanded spectrum agents such as voriconazole and posaconazole, some of these rare pathogens remain poorly responsive also to several of the newer agents.

The true incidence of stomatologic fungal infections in the immunocompromised population is not clearly known, but is estimated to be very low, with the most common cause being *Candida* species [9]. Oral localization may be primary (by oral pathogens such as *Aspergillus* species, zygomycetes) or secondary to systemic fungal disease. Pertinently, apart from the commonly implicated pathogens such *Candida* and *Aspergillus*, infection with

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the normally avirulent, saprophytic fungi including *Geotrichum, Fusarium, Rhodotorula, Saccharomyces* and *Penicillium* species are being increasingly identified as oral pathogens, with significant implications in choice of therapy and prognosis [10].

A clinical conundrum is being able to distinguish disseminated fungal infections from leukemia cutis. Both entities have similar clinical presentations and may temporally co-occur in the same patient, rarely occurring at the same location [11]. Therefore, confirmation requires a histological examination. In this report, we describe a case of acute myelogenous leukemia (AML) complicated by necrotic gingival and cutaneous lesions, which were later attributed to be fungal in etiology.

2. Case report

A 62 year-old female with a history of myelodysplastic syndrome (MDS) transformed to AML was admitted with shortness of breath after receiving two units of red blood cell (RBC) transfusion. She was first diagnosed with MDS 2 years previously when she was found to be pancytopenic during a pre-operative evaluation for elective knee repair. She remained transfusion independent and was observed for her MDS, until 3 months prior, when she had a repeat bone marrow evaluation for worsening cytopenia. Bone marrow revealed leukemic transformation with 51% myeloid blasts and mutations in *TP53, NRAS, NOTCH, TET2*, and complex cytogenetics. She was then induced with cladribine, idarubicin, cytarabine (CLIA). She did not respond to CLIA and was transitioned to a 10-day decitabine regimen. She was admitted 30 days into her second cycle of decitabine, with continued severe neutropenia since completing her first decitabine course.

On admission, she reported gingival pain and oral lesions which were first noticed a month prior to admission. The patient had developed sublingual ulcerations two weeks prior to admission, typical of those arising from chemotherapy began 4 weeks prior to admission. Upon admission she reported that the original lesions had largely resolved, but that she now had new lesions along the anterior gingival-dentition margins near both the upper and lower incisors. Of note, the patient had undergone numerous prior dental restorations such as fixed bridges and crowns on the anterior mandible. The lesions appeared necrotic with yellow-white tinted tissue along the buccal-facing gingival tissue at the base of her upper and lower incisors, and in the premaxillary region nearest the interincisal papillae. There was also gingival hyperplasia adjacent to these regions. Laboratory findings on admission included profound trilineage pancytopenia (Table 1). A maxillofacial CT scan was performed and showed fat stranding over the anterior mandibular buccal gingiva, and a bony defect immediately adjacent to it concerning for osteomyelitis (Fig. 1). A biopsy was requested, to help distinguish between infection and leukemic infiltrate, but was not performed due to concerns about bleeding from the patient's profound thrombocytopenia. She was started promptly on empiric broad spectrum antimicrobials, including antifungal coverage with caspofungin and posaconazole. Unfortunately, her oral lesions continued to progress very slowly over the next ten days despite continued antimicrobial therapy and oral rinses with keratinocyte growth factor support. Attempts at improving absolute neutrophil (ANC) counts with filgastrim proved unsuccessful. Approximately 10 days into admission she developed new skin lesions on her forehead and shoulders, raising a concern for disseminated fungemia versus leukemia cutis. Pathology of the oral tissue, sampled 23 days post admission, showed necrotic gingival tissue with numerous septate hyphae staining positive for GMS stain (Fig. 2). A concurrent skin biopsy also demonstrated GMS positive angioinvasive septate organisms with constricted hyphae and dilated chlamydoconidia morphologically raising the possibility of *Fusarium* sp. (Fig. 3). Additionally, chest imaging showed multiple nodular pulmonary lesions suspicious for multifocal fungal infection. Antifungals were expanded to include intravenous liposomal amphotericin, voriconazole and posaconazole for better *Aspergillus* and *Fusarium* coverage and white blood cell (WBC) transfusions were begun to help improve her WBC counts against the infection. A week after collection the skin biopsy tissue culture grew *Fusarium* species. Due to limited tissue material, the oral tissue biopsy was not sent for culture. Nevertheless, she showed an impressive improvement in her oral and skin lesions a week into receiving 3 sessions of WBC transfusions along with antifungal therapy. Unfortunately, two weeks into therapy, the patient developed sudden onset of shortness of breath which progressed to fatal hypoxic respiratory failure. Autopsy was not performed.

3. Discussion

Fusarium species typically cause superficial skin infections in immunocompetent patients but may present as disseminated infections, especially in the immunocompromised, hematological malignancy population [12,13]. After *Aspergillus, Fusarium* is the second most common cause of invasive mold infections in immunocompromised patients [10,14]. Main portals of entry for this pathogen include the skin and the sino-pulmonary tree [13]. Risk factors for *Fusarium* include persistent granulocytopenia, T-cell lymphocyte depletion and previous fungal infections [15]. Oral invasive *Fusarium* infection has only rarely been described to occur as a necrotic gingival ulceration extending into the alveolar bone in a neutropenic patient [16]. More often, the infection is limited to the sinuses and does not involve an oral element [17]. Two important characteristics consistent with diagnosis of *Fusarium* infection include the blood cultures growing mold and the presence of skin lesions [13]. While none of the blood cultures grew mold, our patient had multiple skin lesions with a positive skin biopsy culture strongly supportive of *Fusarium* infection. Because the narrow, dichotomously branching, septate hyphae of *Fusarium* share morphological similarities with other fungi including *Aspergillus* and *Scedosporum,* differentiation often requires immunohistochemistry [18] and

special in-situ hybridization techniques to be performed on paraffin-embedded tissue specimens [19,20] or microbiology culture. These techniques are especially useful when the cultures for identifying the mold return negative. Of note, beta-glucan assays are not specific for *Fusarium*, and *Aspergillus* galactomannan assays cross-react with *Fusarium* [21,22]. Therapy should be instituted promptly based on supportive findings since species identification is often not available immediately.

Distinguishing gingival fungal infection clinically from gingival leukemic infiltration can be challenging. Gingival leukemia generally presents with erythematous or cyanotic gingival hyperplasia with or without necrosis, petechiae, ulcers, and hemorrhage and is more common in the acute myelomonocytic leukemia [23,24]. Our patient did have focal areas of sharply demarcated, necrotic appearing lesions with surrounding gingival hyperplasia with CT image findings concerning for leukemic infiltration.

Invasive *Fusarium* infection is associated with a very poor prognosis and outcomes are heavily dependent upon immune system recovery. Therapy entails prompt institution of systemic broad-spectrum antifungal therapy. Combination therapies including the lipid formulation of amphotericin B and voriconazole are preferred over monotherapy, especially in patients who are severely immunocompromised or with severe fungal disease, due of the variable susceptibility of *Fusarium* species to antifungal agents [25]. Successful outcomes have been reported with other azole agents such as posaconazole, isavuconazole [26,27]. Surgical debridement

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