Malassezia furfur Folliculitis in Cancer Patients
The Need for Interaction of Microbiologist, Surgical Pathologist, and Clinician in Facilitating Identification by the Clinical Microbiology Laboratory*

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ABSTRACT

Malassezia furfur (MF) is a lipophilic yeast which can be found as a member of the indigenous microbiota of human skin. In immunocompromised transplant patients, MF can cause a distinctive folliculitis which is a clinical look-alike to Candida folliculitis, the latter of more potentially devastating significance. Recovery of MF in culture is dependent upon the addition to culture media of an exogenous source of fatty acids, such as olive oil. The addition of an extra Sabourauads plate with an olive oil overlay to the routine set of media used to inoculate all skin biopsy specimens in order to detect MF is labor-intensive and not cost-effective. Thus, MF may not be isolated in cases of MF folliculitis unless the clinical microbiology laboratory is put on alert by the clinical suspicions of the attending physician, or by histopathologic findings suggestive of folliculitis revealed by review of surgical pathology slides. The clinical, pathological, and microbiological findings of two cases of MF folliculitis are presented where an interactive approach featuring communication between the microbiologist, the surgical pathologist, and the clinician guided the microbiology laboratory to the isolation and identification of isolates of MF that were clinically-relevant. These cases underscore how a combined approach which features communication between the laboratory and the clinical services always provides superior guidance in the diagnosis and therapy of infectious diseases.

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Introduction

Malassezia furfur (MF) is a lipophilic yeast, which is a member of the indigenous microbiota of the skin of many warm-blooded hosts.\(^5\) Growth of MF on culture media is dependent upon the addition of an exogenous source of medium- to long-chain fatty acids, such as olive oil.\(^5\) Malassezia furfur can cause an erythematous papulopustular folliculitis that may be more common than is recognized in immunosuppressed patients\(^4,5,7\) and which must be differentiated from the macronodular lesions of disseminated candidiasis, as well as other conditions.\(^1,5,6,7\) Since distinction from these other conditions on purely clinical grounds is not always feasible, one alternate approach to diagnosis would be to add an extra Sabourauds plate with an olive oil overlay to the routine set of media inoculated with specimens from the skin.

This global approach, however, would be labor-intensive and neither wise nor cost-effective, since the mere recovery of MF from skin biopsies may be hard to interpret in the absence of clinical suspicion, patient history or of histopathological findings suggestive of a frank folliculitis. Subsequently, an interactive approach which features communication between the microbiologist, the surgical

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**Figures 1A and 1B.** The clinical manifestations of Malassezia furfur (MF) folliculitis in the two described patients were similar: an erythematous, pruritic, papulopustular rash on the back and shoulders, which can be appreciated in low and high magnification photographs. Some lesions became unroofed and were replaced by scabs. The raised (papular) character of these lesions can be appreciated in the high-power photograph.
pathologist and the clinician would appear to be the most reasonable way in which to guide the laboratory staff towards isolation and identification of clinically-relevant isolates of this organism, while decreasing labor and cost.

Case reports of two patients with follicular rashes will be presented which illustrate the convenience of such an interactive approach, without which isolation and identification of MF as the etiological agent of folliculitis in these two patients would have been missed.

Materials and Methods

Tissues from skin biopsy specimens submitted to microbiology for fungal culture were inoculated onto Sabouraud's dextrose agar (SAB), SAB with chloramphenicol, and brain heart infusion agar. All were incubated at 30°C. For isolation of MF, a few drops of sterile olive oil were added to the SAB plate. Tentative identification of MF was carried out by the observation of growth in the presence, but not in the absence, of olive oil. Definitive identification relied on colonial morphology suggestive of a yeast, direct smears of colonial growth with the expected microscopic morphology, lack of reactivity in the Vitek YBC yeast identification card* and positive results fol-

* Vitek Systems, Hazelwood, MO.
allowing the rapid urea test. Skin biopsy specimens sent to surgical pathology were formalin-fixed, paraffin-embedded, and stained with hematoxylin and eosin (H & E), gomori-methenamine silver stain (GMS), and periodic acid-Schiff stain (PAS).

Case Reports

Case #1

A 34-year-old white female with breast cancer metastatic to bone was first diagnosed in January 1991. The patient had initial response to cyclophosphamide, adriamycin, and 5-fluorouracil systemic chemotherapy but showed progressive disease by October 1991, as evidenced by increased bone pain, worsening metastatic disease on bone scan, and rising tumor markers (CEA and CA 15-3). The patient was referred to the H. Lee Moffitt Cancer Center at the University of South Florida and relapse therapy was begun with standard dose ifosfamide, carboplatinum, and etoposide. After documenting response the patient underwent peripheral stem cell harvest after intravenous cyclophosphamide.

The patient was admitted to the bone marrow transplant unit on April 1, 1992 for high dose chemotherapy and peripheral blood stem cell rescue. Treatment was begun with high dose ifosfamide, carboplatinum, and etoposide for six days. Treatment was delivered in a single patient hospital room equipped with laminar air flow and HEPA filters. Nystatin was used for oropharyngeal Candida antigen, and aerosolized pentamidine for Pneumocystis carinii prophylaxis. No systemic antibacterial or antifungal prophylaxis was utilized.

Upon admission, the patient was found to be well developed and in no acute distress. She was afebrile with stable vital signs. No skin rash or lesions were seen. There was no adenopathy. Admission laboratory exam revealed a white blood cell (WBC) count of 3,100 and an actual neutrophil count (ANC) of 2,100. Renal and liver functions were normal. Preadmission scans revealed boney metastatic disease and were otherwise unremarkable.

Therapy was begun with high dose ifosfamide, carboplatinum, and etoposide for six days. Treatment was delivered in a single patient hospital room equipped with laminar air flow and HEPA filters. Nystatin was used for oropharyngeal candidiasis prophylaxis, and aerosolized pentamidine for Pneumocystis carinii prophylaxis. No systemic antibacterial or antifungal prophylaxis was utilized.

In order to minimize the risk or relapse, the patient was admitted to the bone marrow transplant unit in July 1992 for high dose chemotherapy and autologous bone marrow transplantation. On admission, examination revealed the patient to be a well developed, well nourished young female in no distress. There were no skin rashes or lesions. Head and neck exam showed resolution of the mandibular tumor and no other abnormalities. Admission laboratory evaluation revealed WBC, 7,200 and ANC, 6,300. Chemistry panel was unremarkable with normal renal and liver functions. Preadmission computerized tomography showed resolution of previous adenopathy.

Upon admission, the patient underwent harvest of 922 ml of bone marrow from the posterior iliac crests. The following day she began high dose chemotherapy with ifosfamide, carboplatinum, and etoposide given daily for six days. After two days of rest for drug elimination, cryopreserved bone marrow was thawed and reinfused intravenously.

The patient tolerated chemotherapy relatively well except for nausea controlled with antiemetics and dexamethasone. Peripheral blood counts fell and the patient had her first fever to 38°C the day before transplantation. Cultures were obtained and broad spectrum antibiotic coverage with ceftazidime and vancomycin was begun. The day following transplantation a follicular skin rash over the shoulders, neck and back appeared (figure 1A & 1B). Fevers persisted and metronidazole was added for anaerobic coverage with development of enteritis and mucositis. Owing to persistent fevers, empiric antifungal coverage with amphotericin B was begun five days post-transplant. By this time, the skin rash had begun to resolve. Skin biopsy suggested fungus; however, the rash had significantly improved before cultures of the skin biopsy grew Malassezia furfur. By day 10 post transplant, WBC was 1,200 and the ANC was >500 per mm³. The patient defervesced and was subsequently discharged from hospital 19 days post-transplant with her rash resolved.

Case #2

A 22-year-old white female presented with a history of Burkitt's lymphoma of the distal ileum diagnosed at laparotomy. After resection of the tumor, the patient was treated with five cycles of cyclophosphamide, adriamycin, vincristine, and prednisone along with prophylactic intrathecal methotrexate. The patient did well off therapy from January to March 1992 when she was noted to have a mandibular and intra-abdominal relapse with retroperitoneal and mesenteric adenopathy. Reinduction was accomplished with high dose cytosine arabinoside and cisplatinum in April 1992. The patient subsequently was referred to the H. Lee Moffitt Cancer Center and received two cycles of standard dose chemotherapy with ifosfamide, carboplatinum, and etoposide achieving a complete remission.

In order to minimize the risk of relapse, the patient was admitted to the bone marrow transplant unit in July 1992 for high dose chemotherapy and autologous bone marrow transplantation. On admission, examination revealed the patient to be a well developed, well nourished young female in no distress. There were no skin rashes or lesions. Head and neck exam showed resolution of the mandibular tumor and no other abnormalities. Admission laboratory evaluation revealed WBC, 7,200 and ANC, 6,300. Chemistry panel was unremarkable with normal renal and liver functions. Preadmission computerized tomography showed resolution of previous adenopathy.

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By completion of chemotherapy, two days before transplantation, WBC had fallen to 2,000 and a follicular rash was noted on the shoulders. The first fever occurred on the day of transplantation and empiric broad spectrum coverage with ceftazidime
and vancomycin was begun after cultures were obtained. The follicular rash had spread to involve the upper chest but was otherwise asymptomatic. Daily fevers from 38°C to 38.5°C persisted, and metronidazole was added for anaerobic coverage in the setting of worsening mucositis. Skin biopsy was obtained and clotrimazole cream was begun. Owing to persistent fevers in the setting of prolonged neutropenia, empiric antifungal coverage was initiated 10 days after transplant with fluconazole. By this time, the follicular rash had already begun to fade before systemic antifungal therapy had been started. Over the next week the rash continued to resolve and bone marrow recovered with an ANC of >500 per mm$^3$ by day 18 after transplantation. All antibiotics were discontinued and the patient was discharged for outpatient followup. The rash had begun to fade once culture results identified Malassezia furfur.

Microbiologic and Pathologic Findings

Tissue sent to microbiology from the skin biopsy on patient #1 failed to show growth after two days of incubation in the absence of olive oil (figure 2A). At that time, review of the H & E slides by the microbiologist, upon requests by the surgical pathology resident, revealed acute fungal folliculitis, with fibrinoid necrosis of one of the walls of the hair follicles, but without inflammatory cells. Within the infundibulum of the hair follicle in the necrotic areas, there were multiple round yeasts which were highlighted by the PAS (figure 3) and GMS stains. The yeasts were small with unipolar and broad-based budding, and a small circumferential thickening at the bud attachment. Hyphae and pseudohyphae were absent.

Given such histopathologic findings suggestive of MF, the microbiologist requested that the medical technologist add a few drops of sterile olive oil to the plates and spread them over the inoculum. Within two days following olive oil addition, the previously negative fungal plates were overrun with small, white, creamy colonies of variable sizes (figure 2B). A wet mount prepared from the growth on the plate showed small yeasts with unipolar and broad-based budding, and collarettes. The VITEK YBC cards were set up and were completely unreactive. A rapid urea test was set up and the medium turned positive (red-pink) within a few hours. Besides MF, several species within the genera Cryptococcus, Rhodotorula, and Trichosporon are also urease positive. The latter three genera, however, can be ruled out on the basis of: (1) growth in the absence of added olive oil, (2) their own particular colonial and microscopic morphologic characteristics, and (3) specific patterns of reactivity in the VITEK YBC card.

Specimens from the skin biopsy on case #2 were inoculated onto fungal media with olive oil from the start, given the clinical suspicion of the astute clinician who alerted the microbiologist prior to the biopsy procedure. Within three days, yeast colonies were identified with characteristics identical to those of patient #1. The surgical pathology specimen from patient #2, however, failed to reveal the presence of fungal microorganisms.

Discussion

Malassezia furfur is a common lipophilic fungal saprophyte of human skin that is known to cause the superficial dermatosis tinea (or pityriasis) versicolor, as well as a distinctive folliculitis. On occasion, a deep-seated infection may occur particularly in debilitated hosts with central catheters who are receiving intravenous lipid therapy. Several studies have established the high incidence of MF skin carriage on normal-appearing skin of the scalp, shoulders and chests of adults.

The entity of MF folliculitis is probably a more common clinical problem than is currently appreciated and is of particular importance to clinicians because of its potential for confusion with life-threatening fungal infections. It occurs predominately in post-adolescents as opposed to acne vulgaris which it
Figures 2A and 2B. Tissue from the skin biopsy on patient #1 was cultured on Sabourauds dextrose agar (SAB) medium but failed to show growth after two days of incubation at 30°C in the absence of olive oil (2A). Two days following the addition of a few drops of sterile olive oil to the same plate, it became overrun with small, white creamy colonies of variable size (2B).
As represented by both cases, lesions of MF folliculitis are usually multiple and are distributed over the back, shoulders and/or upper chest. Many patients with MF folliculitis have underlying debilitative diseases or conditions, such as diabetes mellitus, cancer, bone marrow transplantation, and steroid or broad-spectrum antibiotic administration. Biopsy of affected hair follicles shows a spectrum of pathological findings, from plugging of the hair follicle to frank destruction of the follicular wall with fibrinoid necrosis, as seen in patient #1. An infundibular infiltrate consisting of polymorphonuclear and mononuclear leukocytes may or may not be present and was absent in patient #1.

Within the hair follicle, numerous budding yeasts are usually present without hyphal or pseudohyphal forms, as opposed to Candida which features both filamentous and yeast forms in tissue in cases of deep or disseminated infection (figure 3). An intensely pruritic eosinophilic pustular folliculitis associated with abundant MF yeasts inside hair follicles has also been associated with AIDS patients. Studies utilizing electron microscopy have suggested that follicular occlusion may be a primary event in the development of MF folliculitis, with yeast overgrowth as a secondary phenomenon. The lesions of MF folliculitis are to be contrasted with those of disseminated candidiasis, which are clinical look-
alikes but are of a much graver significance.\textsuperscript{1,5,6} The macronodular lesions of disseminated candidiasis may be located anywhere on the body but have predilection for the extremities, whereas candidal papulopustulosis is most commonly found in heroin addicts and most frequently in the bearded area, shoulders, and chest.\textsuperscript{5} \textit{Candida} also favors intertriginous moist areas such as the groin, axilla and skin folds, particularly in diabetics and obese patients. Satellite lesions are common as well. Both types of candidal lesions yield the responsible fungus if biopsy material is placed on standard fungal culture media, whereas tissue from MF folliculitis requires the lipid supplementation already alluded to. Surgical pathological examinations in MF folliculitis may disclose the presence of yeasts within the follicular infundibulum and perhaps within the surrounding epidermis, but without the deep dermal invasion which may be observed frequently with infections by \textit{Candida}.\textsuperscript{6} Destruction of the hair follicle is also possible.

The approach followed in the clinical microbiology laboratory at our institution is a conservative one. It relies on feedback from the surgical pathology resident or attending, and/or clinical attending or fellow, in order to alert the laboratory that a particular specimen from skin is to be tested for the presence of this organism. This is superior to any approach requiring that an additional fungal plate with an olive oil overlay be part of the work-up of all skin biopsy specimens. This approach can be adapted by some institutions, and is perhaps already being practiced in many others. It underscores to laboratorians that a combined approach to patient care, where continual communication exists between pathology and the clinical services, provides superior guidance in the diagnosis and therapy of infectious and neoplastic diseases.

References


