Mycotic cervical lymphadenitis following oral mucositis in children with leukemia

Four children developed mycotic cervical lymphadenitis while receiving cytotoxic chemotherapy for acute leukemia. Neutropenia, oral mucositis, and broad-spectrum antibiotic administration preceded the appearance of lymphadenitis in each case. Enlarged tender cervical lymph nodes of mycotic origin were not clinically distinguishable from lymphadenitis of bacterial or viral origin. Although cervical lymphadenitis was the initial clinical manifestation of deep fungal infection, computerized tomography of the chest and abdomen subsequently demonstrated asymptomatic pulmonic, splenic, or hepatic lesions characteristic of fungal abscesses in all four children. These findings demonstrate the importance of microbiologic identification of the etiologic agents of cervical lymphadenitis following mucositis and neutropenia in children with leukemia. (J PEDIATR 106:243, 1985)

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ALTHOUGH CERVICAL LYMPHADENOPATHY may be of noninfectious origin, in the absence of supraclavicular adenopathy, prolonged fever, weight loss, and fixation of the lymph node to the overlying skin this disorder is most often of bacterial, viral, or protozoan origin.1-4 Rarely, cervical lymphadenitis has been attributed to infection with fungi including Coccioidoides immitis, Histoplasma capsulatum,1 Aspergillus species,1 and Cryptococcus neoformans.6 Candida species frequently colonize the oropharynx, but this organism has been conspicuously absent from reported causes of cervical lymphadenitis.2-4 To our knowledge, only one case of cervical lymphadenitis caused by Candida species has been reported.7

We describe four children with acute leukemia who developed mycotic cervical lymphadenitis following episodes of neutropenia and moderate to severe oral mucositis. Candida species were responsible for the lymphadenitis in three of the four children.

METHODS

Patients with mycotic cervical lymphadenitis were identified by a computer-assisted review of the discharge diagnoses of all patients treated at St. Jude Children's Research Hospital from February 1962 to March 1, 1984. Only patients in whom biopsy or aspirate of cervical lymph nodes yielded histologic or microbiologic evidence of mycotic infection were included in this report.

Neutropenia was defined as <500 neutrophils per cubic millimeter of blood.

CASE REPORTS

Patient 1. This 5-year-old white girl was admitted to the hospital with acute nonlymphocytic leukemia. Broad-spectrum antibiotics were administered during the first 4 weeks of remission-induction chemotherapy because of persistent fever and neutropenia. Amphotericin B (1 mg/kg/day) was administered empirically during the last 10 days of this period of neutropenia. Fever resolved 3 days after the initiation of amphotericin B therapy. Remission of the leukemia occurred 5 weeks after admission.
Two months after the diagnosis of leukemia the patient again developed fever and neutropenia after a pulse of chemotherapy. Oral candidiasis and mucositis were evident, and throat cultures remained positive for *C. albicans* despite the use of nystatin orally. Defervescence occurred after 1 week of broad-spectrum antibiotic administration, but a right-sided anterior cervical lymph node 2 cm in diameter had developed by the end of this antibiotic course, concurrent with neutrophil recovery. Over the next 2 weeks this node enlarged further and became tender. The node was biopsied, and Gomori methenamine silver staining revealed rare yeasts with pseudohyphae. Culture of the biopsied tissue yielded *C. albicans* and *Staphylococcus epidermidis*. Computerized tomography of the abdomen revealed a few hypodense lesions characteristic of fungal abscesses within the spleen. Amphotericin B was administered for 6 weeks together with 5-fluorocytosine (4500 mg/m²/day) for the first 4 weeks. Repeat CT scan of the abdomen at the end of the antifungal course revealed resolution of the splenic lesions. Three months after appearance of the cervical lymphadenitis, resolution was almost complete.

**Patient 2.** This febrile, neutropenic 9-year-old white girl was admitted to the hospital with acute nonlymphocytic leukemia, and broad-spectrum antibiotic therapy was initiated. Oral mucositis was evident after the first week of remission-induction chemotherapy. One week later a tender left-sided submandibular lymph node 1 cm in diameter appeared; throat culture yielded *C. albicans*. Three days later the left node had enlarged further and an enlarged right submandibular node appeared; amphotericin B was administered empirically. Fever and neutropenia resolved during the next week, and the submandibular nodes became smaller. Bone marrow examination then revealed remission, and antimicrobial therapy was discontinued. However, within 1 week bilateral cervical node enlargement recurred. Gram stain of necrotic material obtained by aspiration of the left node revealed no organisms, but PAS light green stain revealed yeasts with pseudohyphae. Culture of the aspirated material grew *C. albicans*. Amphotericin B therapy was re instituted; 3 weeks after initiation of this second course of amphotericin B the left node had become smaller but the right node had enlarged. 5-Fluorocytosine therapy was added, but both drugs were discontinued 1 week later because of renal impairment. Miconazole (20 mg/kg/day) was administered for the next 6 weeks. During this time, incision and drainage of the right node yielded culture-negative pus, with yeasts visualized by special fungal stains. Chemotherapy was continued, and cervical lymph node infection persisted; frequent incision and drainage of fluctuant nodes were required. At the end of 10 months, the patient developed fever without any apparent source and unresponsive to broad-spectrum antibiotic therapy. Computerized tomography of the abdomen then revealed the appearance of multiple hypodense lesions in the liver and spleen characteristic of mycotic abscesses. Gram stain of a biopsy specimen of one of the hepatic lesions revealed no organisms, and culture was negative, but Gomori methenamine silver and PAS light green stains revealed yeasts with pseudohyphae. The patient was again given amphotericin B and 5-fluorocytosine for 5 weeks, and no further chemotherapy was administered. Cervical adenopathy persisted for the next 7 months, at which time repeat CT scans of the abdomen suggested the presence of new hepatic lesions. Ketoconazole (200 mg/m²/day) was then administered for 4½ months, after which CT scan of the abdomen revealed no new lesions and calcification of the previously visualized hepatic and splenic lesions. Cervical adenopathy has continued now for longer than 1½ years since this course of ketoconazole, but there has been no further evidence of deep organ involvement with fungi.

**Patient 3.** This febrile, neutropenic 4-year-old white boy was admitted to the hospital with acute nonlymphocytic leukemia, and remission-induction chemotherapy was initiated. Prompt lysis of fever followed treatment. Two weeks after admission, oral mucositis was evident, and despite continued antibiotic administration, fever recurred. Amphotericin B was administered empirically for 1 week, at which time lysis of fever occurred, with resolution of neutropenia and bone marrow remission.

Three months later the patient was admitted with fever during a period of neutropenia induced by a pulse of cytotoxic chemotherapy. Oral mucositis was evident. Because of lack of response to broad-spectrum antibiotic administration and in the presence of heavy colonization with *C. albicans*, empirical therapy with amphotericin B was initiated, but was discontinued after 1 week because CT scan of the abdomen revealed no abnormalities and fever and neutropenia had resolved. Four days later an enlarged left-sided anterior cervical node was evident. Despite 5 days of antibiotic therapy, fluctuation and erythema developed. Gram stain of aspirated material from the node yielded budding yeasts with pseudohyphae, but culture was sterile. Computerized tomography of the chest and abdomen revealed multiple bilateral nodular palmonic lesions characteristic of mycosis. Cervical adenopathy and pulmonary lesions responded to a 4-week course of amphotericin B and 5-fluorocytosine. The patient received a 4-week course of ketoconazole during his next pulse of aplasia-inducing chemotherapy in an attempt to prevent recurrence of disease. Three months after completing this course of ketoconazole, a necrotic scalp lesion 2 cm in diameter appeared. Biopsy of this lesion revealed branching septate hyphae, and culture grew *Aspergillus flavus*. A 3-week course of amphotericin B was administered, and the lesion resolved.

**Patient 4.** This 3-year-old white girl was admitted to the hospital with acute lymphocytic leukemia. Two weeks after initiation of remission-induction chemotherapy, fever and gingivitis occurred in association with neutropenia. *C. albicans* was cultured from the throat despite administration of nystatin and gentian violet. Fever with neutropenia continued for 1 month and was unresponsive to broad-spectrum antibiotic therapy. Amphotericin B therapy was administered for 4 days, but was discontinued when the neutropenia resolved. One week later the patient was afebrile, but pneumoperitoneum developed. Exploratory laparotomy revealed multiple perforations of the distal ileum and cecum; the involved intestine was resected. One week postoperatively and during remission, fever recurred and an enlarged firm left-sided anterior cervical lymph node appeared, and subsequently became fluctuant. Mycotic organisms were poorly visualized in the aspirated material with Gram and Wright-Giemsa stains, but Gomori methenamine silver as PAS light green stains revealed large branching septate hyphae. The presence of dichotomous branching, dark-staining septations and dysjunctors indicated that this organism was likely a member of the dematiaceous group of fungi.
No organism was isolated by culture. An enlarged right-sided cervical node also became evident, and miconazole therapy was begun. Computerized tomography of the abdomen revealed multiple hypodense areas in the liver and spleen indicative of fungal abscesses. After 5 weeks the cervical adenitis resolved, but CT scan revealed no change in hepatic and splenic lesions. Because of the lack of response to antifungal therapy, needle aspirates of the liver were obtained, but failed to demonstrate any organisms on two occasions. 5-Fluorocytosine was administered for 7 months, and was discontinued when there was no further clinical evidence of mycoses.

**DISCUSSION**

Patients receiving cytotoxic chemotherapy for the treatment of leukemia and other cancers frequently develop neutropenia and mucositis with oral, esophageal, and gastrointestinal ulcers. Moreover, the microbial flora of the alimentary tract of these patients is often significantly altered because broad-spectrum antibiotic administration during episodes of fever and neutropenia favors colonization with *Candida* species and other antibiotic-resistant fungi. Consequently, this population is at increased risk to develop invasive mycotic infections. Despite the prediction of these patients for mycotic infections, especially candidiasis, we are not aware of any reports of candidal cervical lymphadenitis in patients with malignancies. The single reported case of candidal cervical lymphadenitis occurred in an infant with chronic granulomatous disease.

The administration of broad-spectrum antibiotics and the occurrence of neutropenia with marked oral mucositis preceded the appearance of mycotic cervical lymphadenitis in each of our four patients. Chemotherapy-induced oral ulcers likely permitted circumvention of the specific and nonspecific host defenses that normally prevent candidal invasion in the presence of oral moniliasis. Once fungi penetrated the initial host defenses and invaded the cervical lymph nodes, immunosuppression of the cellular elements of the immune system may have favored mycotic growth within the lymph node, resulting in fungal nodal abscesses and dissemination of the infection. Although preventive measures such as oral administration of nystatin and gentian violet may reduce the incidence of systemic mycosis, the use of these agents did not preclude the development of mycotic cervical lymphadenitis in our patients.

Mycotic cervical lymphadenitis is not clinically distinguishable from lymphadenitis of bacterial, viral, or toxoplasmal origin. Furthermore, even after lymph node biopsy, fungi may easily be overlooked; mycotic organisms are often not evident or only poorly visualized with Gram stain and frequently cannot be grown in culture. Mycotic organisms may become evident only with the use of special fungal stains; visualization of structural detail may permit tentative identification of the infecting species. Thus, Gomori methenamine silver or PAS light green stains appear to be very useful in the diagnosis of mycotic lymphadenitis and should be included in the evaluation of lymph node biopsies when the specimen is sufficient.

The response to antifungal therapy in our patients was gradual at best. The protracted clinical course in patient 2 was reminiscent of the clinical course of atypical mycobacterial infections of cervical nodes, even with appropriate and intensive antifungal therapy, multiple relapses occurred. Although we favor therapy consisting of amphotericin B and 5-fluorocytosine, the oral administration of ketoconazole appeared to be useful in this patient, who did not respond to a prolonged course of amphotericin B and developed compromised renal function.

In patients with leukemia, the appearance of cervical lymphadenitis following oral mucositis and neutropenia should alert the physician to the possibility of systemic mycoses, including involvement of deep organs. Aspiration or biopsy of the involved node should be considered, with special fungal stains such as Gomori methenamine silver or PAS light green used in the evaluation of the tissue specimens. Computerized tomography of the chest and abdomen may be useful in defining the extent of disease if cervical lymphadenitis is of mycotic origin. Our experience suggests that systemic antifungal therapy of ≥1 month duration may be required for resolution of mycotic cervical lymphadenitis in children with leukemia.

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**REFERENCES**