

Chronic Mucocutaneous Candidiasis Associated With Malignant Thymoma and Systemic Lupus Erythematosus With Hypergammaglobulinemia: A Case Report and Literature Review

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Chronic mucocutaneous candidiasis (CMC) is characterized by recurrent candidal infections of the mucous membranes, nails, and skin. Systemic involvement is rare. CMC in adults with coexistent thymoma, benign or malignant, is well-known and is often associated with hypogammaglobulinemia. There is an unusually high frequency of thymoma and systemic lupus erythematosus (SLE). I present a case of a patient with a history of malignant thymoma, SLE, and hypergammaglobulinemia who was found to have CMC. Discussion of the relationship of these findings is presented.

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The association of chronic mucocutaneous candidiasis (CMC) and thymoma is well-known and accepted as a function of T-cell mediated dysfunction.¹ Systemic lupus erythematosus (SLE) and thymoma occur more frequently than one would expect given the prevalence of each disease. The reason for this association has not been identified. Various immunologic findings in the literature are reviewed in an attempt to elucidate the relationship of these diagnoses.

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Case Report

A 44-year-old white man presented to the dermatology department in October 2003 with a 6-week history of discoloration and deformity of his fingernails (Figure 1). His wife frequently removed his cuticles manually, but he had no prior history of nail abnormalities. Fungal culture of the nail plate obtained by another dermatologist 3 weeks earlier revealed *Candida albicans*. Ketoconazole cream applied twice daily to the fingernails 3 weeks prior produced no noticeable change.

Past medical history included SLE (antinuclear antibody 1:320, double-stranded DNA 4.13), hypergammaglobulinemia (total immunoglobulin [Ig] G 2300, IgG1 1220, IgG2 1080, IgG4 303), intermittent oral candidiasis since 2000, hypothyroidism, and malignant thymoma; status post-thymectomy, chemotherapy, and external beam irradiation were completed in April 2003.

On review of systems, the patient had experienced fatigue, a loss of 15 pounds over 2 years, occasional cough with green sputum for 3 years, migratory polyarthralgias and Sjögren syndrome since 1998, and a 3- to 4-year history of a scaly rash on various areas of the body, which resolved spontaneously.

On physical examination, 7 of 10 fingernails exhibited light brown discoloration, proximal onychodystrophy, and distal onycholysis. The sternum demonstrated lightly erythematous yellow-scaled plaques with scalloped borders (Figure 2). The left ear concha demonstrated a lightly scaled erythematous macule. The oral cavity revealed white membranous papules (Figure 3). No lymphadenopathy was present. Microscopic examination of sternal skin scrapings

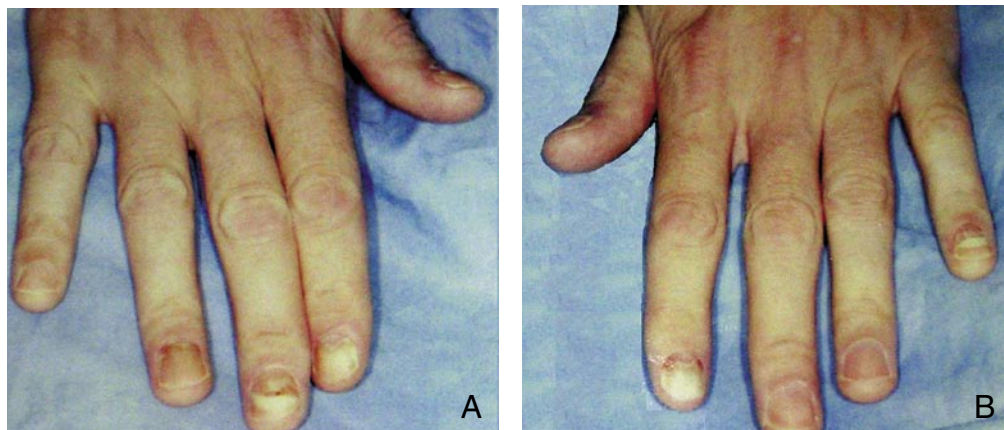


Figure 1. Proximal onychodystrophy and distal onycholysis of several fingernails (A and B).



Figure 2. Lightly erythematous yellow-scaled plaques with scalloped borders on sternum.

revealed multiple pseudohyphae and budding spores consistent with *Candida* spp (Figure 4).

Scaling patches resolved within 2 weeks of application of ketoconazole cream twice daily. Oral lesions resolved with clotrimazole troches. After 2 months of 1-week pulses of itraconazole, all fingernails demonstrated normal growth and appearance proximally.

Discussion

CMC is characterized by recurrent candidal infections of the mucous membranes, skin, and nails with rare systemic involvement.² Four major types are used to classify mucocutaneous candidiasis (Table). The first type is CMC associated with any lethal immune deficiency, often resulting in

only mild oral candidiasis. Severe infection by other organisms usually results in death of the patient by 2 years of age. The second type of CMC is in patients who have a nonlethal immune deficiency. Within this category of CMC, one also may find associated endocrinopathy, most frequently either hypoadrenalism, hyperparathyroidism, or hyperthyroidism. Endocrine failure usually occurs within a few years of the onset of CMC in childhood but may occur in the third or fourth decade of life. A rare variant known as chronic localized mucocutaneous candidiasis is seen in children who develop thick, adherent, hyperkeratotic crusts on the scalp and face, termed *candidal granuloma*.³ The third type of CMC is seen in patients with coexistent thymoma, either benign



Figure 3. Superficial white membranous papules on oral cavity.

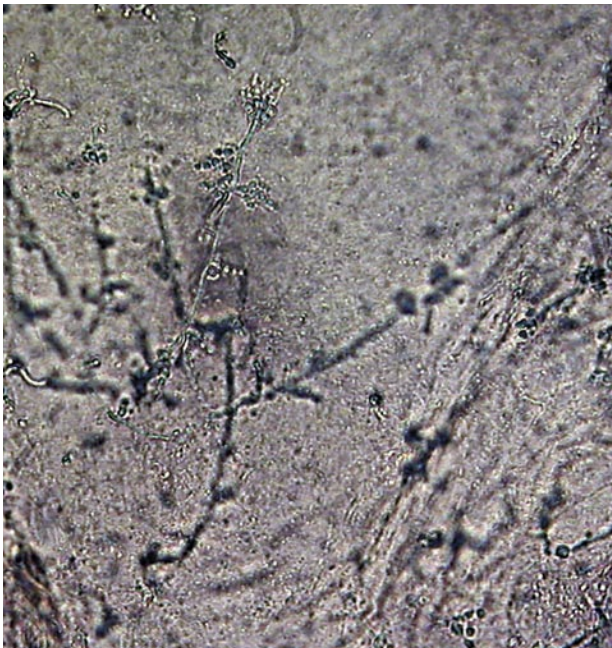


Figure 4. Pseudohyphae and budding spores consistent with *Candida* spp (potassium hydroxide, original magnification $\times 40$).

Categorization of Patients With Chronic Mucocutaneous Candidiasis

Lethal immune deficiency

Nonlethal immune deficiency and endocrine disorders

Thymoma

Acquired immunodeficiency syndrome

or malignant. These patients present with opportunistic infections in the third decade of life or later. The fourth and most common type is CMC associated with acquired immunodeficiency syndrome (AIDS). Other clinical syndromes that have been described separately but have fallen in 1 of 4 major types of CMC include candidiasis with hyper-IgE syndrome, candidiasis with chronic keratitis, familial CMC, and autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.¹ Endocrine disorders often accompanying thymoma include hyperparathyroidism, hyperthyroidism, hypoadrenalism, and panhypopituitarism.⁴

My patient had thymoma-associated CMC with both common and uncommon findings. He was diagnosed in 1998 with SLE by his rheumatologist after developing arthralgias, fatigue, and symptoms of Sjögren syndrome. Antinuclear antibodies were positive at 1:320, but no skin findings were present. He began to develop oral and presumptively cutaneous candidiasis 3 years prior to presentation. Initially, the oral candidiasis was thought to be caused by steroid inhalants for asthma and later oral prednisone for persistent respiratory symptoms. His thymoma was diagnosed in early 2003 after a chest x-ray and chest computerized tomography were ordered for his chronic productive cough unresponsive to several antibiotic courses. An unusual aspect in this patient's history was the presence of hypergammaglobulinemia with thymoma, a finding not previously reported in the literature.

An underlying T-cell defect is accepted as the reason for development of CMC in thymoma patients. Data show that patients with CMC were found to have decreased production of several type 1 cytokines with increased levels of interleukin (IL)-10, the etiology of which is unknown.⁵ These data support the accepted mechanism of a decreased cell-mediated response in patients with CMC.

Various mechanisms by which thymoma may cause immunodeficiency are speculated. There is evidence that T cells in patients with thymoma can inhibit immunoglobulin production. Gatenby et al⁶ isolated a plasma inhibitor of immune function from a thymoma patient with CMC. This inhibitor affected both autologous and normal cell-mediated immune function. Interestingly, removal of the thymoma resulted in disappearance of the plasma inhibitor of immune function but did not reverse the immunologic abnormalities.⁶

Good syndrome is by definition a thymoma with immunodeficiency.⁷ Adults are found to have a combined B- and T-cell immunodeficiency that most often results in hypogammaglobulinemia and reduced to absent B-cell counts. The pathogenesis

is unknown, though studies suggest the bone marrow may be responsible. The 10-year survival of patients with Good syndrome (who rarely have a malignant thymoma) is reported at 33%, with death primarily due to infection or autoimmune disease. Treatment of Good syndrome comprises thymectomy and immunoglobulin replacement as needed.⁷

The frequency of thymoma and SLE, albeit rare, is unexpectedly high. The reason for this association is uncertain.⁸ Schur et al⁹ demonstrated that IL-1 inhibitor produced by monocytes prevents thymocyte proliferation in a mouse model. Patients with SLE produced less IL-1 inhibitor than controls. These findings may indicate that patients with SLE have more potential to allow enhanced thymocyte proliferation, perhaps eventuating in thymoma.⁹ Performing a thymectomy in patients with SLE and thymoma has led to contrasting effects in humans. Both remission and persistence of SLE have been documented and are unpredictable.¹⁰

Conclusion

Key points include examining patients who develop cutaneous or chronic mucosal candidiasis as adults for thymoma and immunologic abnormalities. The pathogenesis of CMC in patients with thymoma is unidentified but is regarded as a cell-mediated defect. The association of SLE and thymoma is rare. Further immunologic studies may elucidate the specific unifying factors in CMC, SLE, and thymoma as the immune system is prominently involved in all 3 conditions. Until then, chronic oral and topical antifungal treatments will be necessary to control the signs and symptoms of patients with CMC. Treatment for CMC includes oral ketoconazole, itraconazole, or fluconazole. Clotrimazole troches are useful, primarily for oral candidiasis. Topical ketoconazole is useful for cutaneous candidiasis.¹¹

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