

Alopecia in Association With Sexually Transmitted Disease: A Review

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GOAL

To develop a better understanding of alopecia related to sexually transmitted diseases (STDs) to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the types of alopecia associated with STDs.
2. Explain the potential causes of alopecia in the presence of STDs.
3. Discuss the STDs that have alopecia associated with them.

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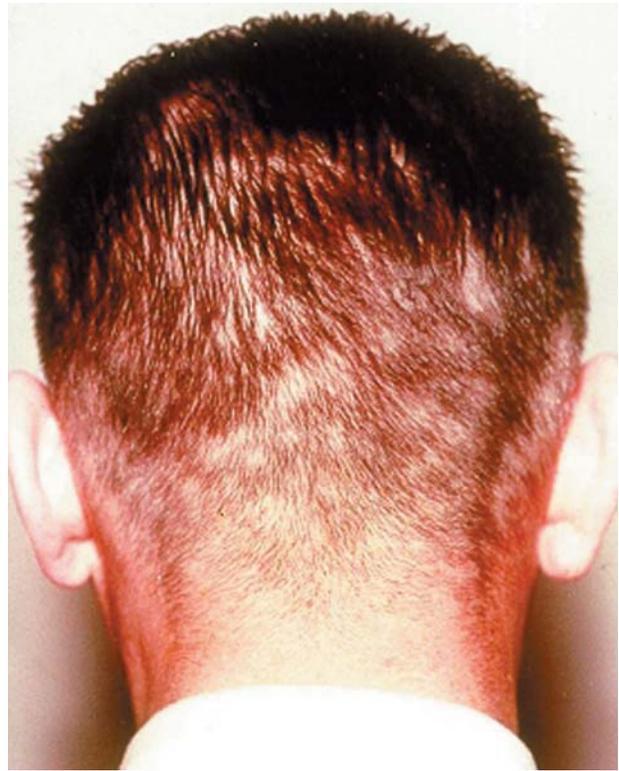
Hair loss has various etiologies. Correct diagnosis of hair disorders is complex and requires the evaluation of clinical presentation, history, physical examination, and laboratory test results. In the patient with a sexually transmitted disease

(STD), alopecia may be an important associated finding and can provide clues to diagnosis. This review focuses on the relationship between hair loss and STDs. Specifically, we review alopecia in association with syphilis and human immunodeficiency virus (HIV) infection and the medications used to treat these infections. In addition, we review the literature regarding the putative association between alopecia areata and cytomegalovirus (CMV). There are multiple mechanisms involved in hair loss in these diseases, including the diseases themselves, systemic sequelae of these infections, autoimmune phenomena, and side effects of medications.

Syphilis

When considering the STDs associated with hair loss, syphilis is usually the first STD described because of the large incidence of the disease and its many reported cases of associated hair loss. This is especially important due to the increasing number of current cases of syphilis. Hair loss does not occur in primary syphilis except when associated with a primary chancre of scalp. Hair loss in secondary syphilis, also known as *latent syphilis*, occurs infrequently; various series report an incidence of 2.9% to 7%.^{1,2} There are 2 types of secondary syphilitic alopecia. The first is an uncommon symptomatic type found in association with an actual secondary lesion (usually papulosquamous) on the scalp. The second is termed *essential syphilitic alopecia*, which designates hair loss in the absence of visible syphilitic scalp lesions. Essential syphilitic alopecia has been divided into 3 types: the classic patchy “moth-eaten” alopecia (Figure), a generalized thinning of the hair, and the moth-eaten type in combination with general thinning of the hair. Of these, patchy moth-eaten alopecia occurs most frequently. The diffuse hair loss of essential syphilitic alopecia as the only manifestation of syphilis is uncommon. Cuzzo et al³ described 2 patients in whom the first sign of disease was alopecia.

Moth-eaten alopecia of syphilis is a characteristic manifestation of secondary syphilis that usually affects the scalp and occasionally other areas such as the eyebrows, beard, and pubic area.⁴ This form of alopecia may be confused with trichotillomania, traction alopecia, and alopecia areata.⁵ Pareek⁴ described a case of an unusual location of patchy moth-eaten alopecia that presented on the anterior side of the lower legs of a 30-year-old man in conjunction with patchy alopecia on the scalp and thinning of the eyebrows. With penicillin administration, hair of the legs, scalp, and eyebrows started to grow; the hair was fully regrown within 6 months, which suggests good prognosis with treatment institution for syphilitic alopecia of all areas.



Moth-eaten alopecia of secondary syphilis.

Jordaan and Louw⁵ systematically documented the histopathologic features of 12 patients with moth-eaten alopecia. Characteristic features included follicular plugging; a sparse, perivascular and perifollicular lymphocytic infiltrate; telogenization; and follicle-oriented melanin clumping.⁵ van der Willigen et al⁶ conducted a study of hair roots in 11 and 8 patients with primary and secondary syphilis, respectively. A decreased number of anagen hair roots; an increased number of catagen hair roots, dysplastic/dystrophic hair roots, and anagen hair roots with sheaths; and more than 20% angulation were observed in both groups.⁶ In addition, Lee and Hsu⁷ noted the histopathologic similarity between alopecia syphilitica and alopecia areata. They reported the histopathologic findings of alopecia syphilitica from 9 patients with secondary syphilis and acute hair loss. The alopecia was moth-eaten in 4 patients and was diffuse but slightly moth-eaten in 5. Microscopically, the dermoepidermal interface was not involved. The number of hair follicles was diminished, with increased numbers of catagens and telogens. Lymphocytic infiltration was present around the hair bulbs and fibrous tracts in 8 patients, and plasma cells were present in 4 biopsy specimens. Except for the follicular changes, the findings resembled those of macular/maculopapular syphilides outside the scalp.

With the follicular changes, the overall patterns closely resembled alopecia areata. Results of the modified Steiner stain did not reveal spirochetes in any of the patients and failed to differentiate between alopecia syphilitica and alopecia areata. Comparing the alopecia syphilitica patients with 13 patients with alopecia areata, the authors found only a few differentiating features. They concluded that the presence of peribulbar eosinophils strongly suggests alopecia areata.⁷ Without peribulbar eosinophils, the presence of plasma cells, abundant lymphocytes in the isthmus, or peribulbar lymphoid aggregates suggests alopecia syphilitica. Elston et al⁸ observed several cases of syphilis with numerous eosinophils in the peribulbar infiltrate and noted that it can be indistinguishable from alopecia areata.

When an associated skin rash or lymphadenopathy is present, the diagnosis of syphilis may be suggested and confirmed by positive serology test results. If such findings are not present, a biopsy specimen to differentiate from other forms of alopecia should be obtained. Because moth-eaten alopecia and alopecia areata have similar resemblance microscopically, syphilis serologic tests are needed.

The treatment of syphilis also has been shown to be a cause of alopecia. Pareek⁹ described the association of syphilitic alopecia and Herxheimer reaction. A 25-year-old man presented with syphilis with widespread thinning of the scalp hair, eyebrows, and pubic area; the scalp showed patchy moth-eaten alopecia. He was treated with 1 to 2 megaunits of procaine penicillin daily for 10 days. Six hours after the first injection, the patient's temperature rose to 103°F; in addition to malaise, headache, flush, and sore throat, he had a transient skin rash and marked loss of hair. All the symptoms disappeared by the next day. Two to 3 weeks later, the lymphadenopathy had disappeared, and the patient's eyebrows and pubic hair started to regrow. The scalp hair was fully regrown 10 weeks from the onset of treatment. The author concluded that diffuse and extensive hair loss after the first injection of penicillin was part of the Herxheimer reaction.⁹

HIV

Hair loss is common in patients with HIV; in black patients, this loss may be associated with hair straightening.¹⁰ Possible causes of hair loss frequently are present in patients with HIV, including chronic HIV infection itself, acute and chronic systemic infections, local infections, nutritional deficits, immune and endocrine dysregulation, and exposure to multiple drugs.¹⁰ Alopecia areata and alopecia universalis also have been reported in patients with HIV.¹¹⁻¹⁴

Smith et al¹⁰ studied and reviewed the clinical and histopathologic features of hair loss in 10 patients with HIV. They noted that the most characteristic change in the hair of patients with HIV was hair loss with straightening, sometimes associated with fine hair texture and an increased tendency for broken hairs. These changes are seen in late-stage disease, most commonly in black patients. Each patient had telogen effluvium, and it was observed that any chronic or acute infection (including HIV) can lead to this condition. Nutritional deficits, often prominent in HIV patients, may lead to or potentiate telogen effluvium. Secondary infections and changes in bowel mucosa may lead to specific nutritional deficiencies even before evidence of clinical wasting is seen. In addition to caloric and protein malnutrition that may affect hair growth, minerals such as copper, zinc, and selenium are decreased in patients with HIV. Elevated levels of interleukin 6 and tumor necrosis factor α , which increase epidermal proliferation, may predispose patients to abnormal keratinization by increasing the proliferative rate and nutritional requirements.¹⁰

Endocrine regulation is another important factor in hair growth. In late-stage HIV disease, androgen levels decrease while estradiol levels increase. Although thyroid hormone levels are normal in advanced HIV, thyroid functions are elevated to more than expected for the amount of wasting and may contribute to the change of hair texture,¹⁰ autoimmune mechanism, associated diseases, and HIV medication side effects.

In the Smith et al¹⁰ study, scanning electron microscopy was performed on plucked and pulled hairs of 10 patients with late-stage HIV-1 infection. In addition, scalp biopsy specimens were examined in both vertical and transverse sections. All patients had telogen effluvium. Numerous apoptotic or necrotic keratinocytes were seen in the upper external root sheath follicular epithelium; a mild to moderate perifollicular mononuclear cell infiltrate, often containing eosinophils, also was seen. Additionally, the mononuclear infiltrate was seen surrounding and within the basaloid cells of the follicles in telogen phase; the midfollicular area had the most marked inflammatory infiltrate. Variable dystrophy of the hair shafts also was a consistent feature. Although telogen effluvium is a common response to a wide spectrum of biologic stresses, the presence of apoptotic or necrotic keratinocytes within the upper end of the external root sheath epithelium, as well as dystrophy of hairs, may be markers of hair loss in patients with HIV-1 infection.¹⁰

Autoimmune alopecia, including alopecia areata and alopecia universalis, can be seen in association

with HIV.¹¹⁻¹⁵ Ostlere et al¹¹ first reported a case of alopecia universalis that developed in a patient 2 years after HIV antibody was detected. The patient showed loss of all scalp hair, eyelashes, eyebrows, and body hair. Two possible mechanisms for the development of alopecia were suggested. The first was that HIV induced nonspecific polyclonal B-cell activation with production of autoantibody either directly or via activated T cells; this supports a humoral theory of alopecia areata pathogenesis. Alternatively, the authors postulated that HIV induced a change in the balance between helper and suppressor cells, which resulted in aberrant cell-mediated immune effect at the hair follicles.¹¹ Werninghaus and Kaminer¹² described a similar patient with alopecia universalis; a biopsy specimen revealed perifollicular fibrosis without inflammation.

Stewart and Smoller¹³ described an HIV-positive patient with altered T-lymphocyte subsets in whom alopecia universalis developed. Results of a skin biopsy of the patient's scalp demonstrated a classic perifollicular lymphocytic infiltrate; results of immunophenotyping of the same specimen revealed that most cells were CD4⁺ lymphocytes. During the active loss of hair, the patient's ratio of CD4/CD8 cells was decreased; however, the ratio normalized during the period of hair regrowth. Their data suggested that systemic immune dysfunction, as seen in HIV infection, may be more important in mediating alopecia areata than localized immune responses. Because of the proposed mechanism of alopecia areata developing in this patient (ie, influx of CD4⁺ lymphocytes to the perifollicular regions of skin when the CD4/CD8 cells ratio is low), the authors were surprised that alopecia areata is not more common in patients with HIV infection.¹³

Cho et al¹⁴ described the association of vitiligo and alopecia areata in patients with HIV. They noted that the development of autoimmune diseases, though not life threatening, is an interesting phenomenon that may result from immune dysfunction or from B-cell infection by HIV, Epstein-Barr virus, or other unknown viruses. They described a 47-year-old man who had vitiligo and alopecia areata approximately 2 years after testing positive for HIV antibodies.¹⁴ Grossman et al¹⁵ described an HIV-seropositive man with acquired eyelash trichomegaly and alopecia areata. They noted that this combination of clinical manifestations is intriguing because the new onset of elongated eyelashes in patients with acquired immunodeficiency syndrome usually has been associated with severe immunosuppression, and alopecia areata has a presumed autoimmune etiology that requires T-cell activation. They concluded that the occurrence of these dichotomous

conditions illustrates the potential selective pathogenesis of progressive HIV infection.¹⁵

Medications used in the treatment of HIV can play a role in hair loss. Geletko et al¹⁶ reported a 33-year-old HIV-infected man who developed alopecia areata after beginning therapy with zidovudine, a nucleoside analogue reverse transcriptase inhibitor. The alopecia reversed after the drug was discontinued. The authors proposed that patients with lower CD4⁺ counts may be more predisposed to zidovudine-induced alopecia than those in the earlier stages of HIV with higher CD4⁺ counts.¹⁶

Indinavir-related alopecia was described by d'Arminio Monforte et al.¹⁷ Of 337 patients given indinavir in combination with nucleoside analogues, 5 patients with HIV developed severe alopecia, which was evident clinically after a mean of 50 days of treatment. All patients were receiving triple therapy that included indinavir. Three patients had diffuse shedding of hair involving the entire scalp, and 2 had circumscribed circular areas of alopecia resulting in complete severe hair loss.¹⁷ Bouscarat et al¹⁸ reported 10 more cases of hair loss associated with indinavir therapy in patients receiving triple antiviral treatment that included indinavir. Hair loss developed during the first 6 months of indinavir therapy and initially involved the lower limbs. Progressive hair regrowth occurred within 4 months after indinavir was replaced by other treatments.¹⁸

Ginarte et al¹⁹ described significant alopecia induced by indinavir plus ritonavir therapy in 3 patients a few weeks after beginning treatment. The authors noted that patients receiving indinavir often experience retinoidlike effects such as alopecia, xerosis, and cheilitis. Nonscarring alopecia can develop in patients receiving indinavir, with or without retinoid effects.¹⁹ Hair loss also has been noted with the use of crivivan.²⁰

CMV

CMV is a prevalent viral pathogen.²¹ Most people with acute CMV experience an inapparent infection. The virus usually is spread through close personal contact, including sexual transmission. There has been debate over the link of alopecia areata with CMV. In 1995, Skinner et al²² described using polymerase chain reaction (PCR) techniques to find evidence of CMV DNA in paraffin block sections of lesions of alopecia areata. Of 21 patient biopsy specimens, 10 had alopecia areata and 11 had other hair loss conditions. Of the 10 alopecia areata samples, 9 were positive for CMV; no other hair loss samples were positive for CMV.²² Skinner et al²³ theorized that CMV may achieve latency in the hair root. Reactivation of CMV was thought to be one of the

pathogenic mechanisms in alopecia areata; the authors argued that a lymphocytic surveillance of not-quite-latent CMV would explain much of the behavior of alopecia areata, which has a tendency for intermittent relapses and remissions.²³

The association between alopecia areata and CMV was refuted by Garcia-Hernandez et al,²⁴ who used 3 different PCR assays to detect CMV DNA in skin punch biopsy specimens of 3 patient groups: 40 patients with alopecia areata, 3 patients with HIV and alopecia areata, and 12 patients with other types of alopecia. PCR assays are known to be the most sensitive assay for CMV detection; this study used different PCR assays to achieve maximum sensitivity for CMV. No CMV DNA amplification was found in any of the specimens.²⁴

Offidani et al²⁵ further contradicted this association. The purpose of their study was to clarify the role of CMV infection and to demonstrate the absence of replication of other autoimmune disease-related herpesviruses (eg, Epstein-Barr virus) in the pathogenesis

of alopecia areata. After extraction of mRNA from tissue samples of 4 patients with active patchy alopecia areata, reverse transcriptase PCR was carried out using primers specific for some viral members of the β Herpesviridae subfamily of the Herpesviridae family (eg, CMV, Epstein-Barr virus, herpes simplex virus). The authors could not detect any replication of the CMV or other β Herpesviridae in the samples collected, which supports the hypothesis that CMV is not the triggering factor in alopecia areata, neither as a reactivator of the immune response nor as a trigger of the autoimmunity.²⁵

Conclusion

Although many etiologies exist for hair loss, STDs should not be overlooked in a sexually active patient presenting with an otherwise unexplainable cause of this condition. A full workup, including clinical history, physical examination, and laboratory tests, should include STDs in the differential diagnosis (Table).

Alopecia and Sexually Transmitted Diseases*

STD	Manifestations and Etiology	Comments
Syphilis	Symptomatic; associated with lesion of secondary syphilis on scalp	Uncommon
	Essential; in absence of scalp lesions: MEA and/or generalized hair thinning	If associated syphilitic skin rash or lymphadenopathy present, confirm diagnosis by positive serology test results. If not present, obtain a biopsy specimen to differentiate condition from other forms of alopecia
	Herxheimer reaction	Marked hair loss after penicillin administration
HIV	HIV infection	Can be found with hair straightening, fine texture, increased tendency for broken hairs; telogen effluvium
	Acute and chronic systemic infections, local infections	Telogen effluvium
	Nutritional deficits	Telogen effluvium
	Immune and endocrine dysregulation	Possible role of androgens, thyroid hormone
	Drugs	Zidovudine, indinavir, ritonavir, crixivan
	AA and alopecia universalis	Polyclonal B-cell activation vs aberrant cell-mediated immune effect
CMV	Possibly AA	

*STD indicates sexually transmitted disease; MEA, moth-eaten alopecia; HIV, human immunodeficiency virus; AA, alopecia areata; CMV, cytomegalovirus.

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