

# Molluscum Contagiosum in Immunocompromised Patients: AIDS Presenting as Molluscum Contagiosum in a Patient With Psoriasis on Biologic Therapy

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## PRACTICE POINTS

- Molluscum contagiosum (MC) is highly prevalent and can have a wide range of atypical clinical presentations in patients with impaired cellular immunity (eg, human immunodeficiency virus [HIV]).
- Treatment of MC should include destructive procedures, if possible, as well as adjunctive agents such as topical retinoids, cantharidin, trichloroacetic acid, imiquimod, or cidofovir.
- Clinicians should consider screening patients with severe recalcitrant psoriasis for HIV to avoid poor outcomes from therapeutic agents.

Molluscum contagiosum (MC) is a common, self-limited cutaneous infection in immunocompetent individuals. However, in immunocompromised individuals the infection often has an atypical presentation and can be difficult to eradicate, making both the diagnosis and treatment challenging. Due to advancements in the management of patients with human immunodeficiency virus (HIV) and cancer, there is a growing population of immunosuppressed individuals, signaling the need for dermatologists to recognize and manage related skin diseases.

We present a case of an atypical MC eruption in a patient on biologic therapy for psoriasis and an unrecognized underlying HIV infection, followed by a current review of the presentation and treatment of MC in various immunosuppressed states. With a growing population of immunosuppressed patients, it is important to recognize MC as a potential indicator of underlying immunosuppression. Testing for HIV should be offered to any patient starting immunosuppressive therapy such as biologic agents.

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Molluscum contagiosum (MC) is a double-stranded DNA virus of the Poxviridae family, which commonly infects human keratinocytes resulting in small, umbilicated, flesh-colored papules. The greatest incidence of MC is seen in the pediatric population and sexually active young adults, and it is considered a self-limited disease in immunocompetent individuals.<sup>1</sup> With the emergence of the human immunodeficiency virus (HIV) and subsequent AIDS epidemic in the 1980s, a new population of immunocompromised individuals has been observed to be increasingly susceptible to MC with an atypical clinical presentation and a recalcitrant disease course.<sup>2</sup> Although the increased prevalence of MC in the HIV population has been well-documented, it has been observed in other disease states or iatrogenically induced immunosuppression due to a deficiency in function or absolute number of T lymphocytes.

We present a case of a patient with long-standing psoriasis on biologic therapy who presented with MC with a subsequent workup that revealed AIDS. This case reiterates the importance of MC as a potential indicator of underlying immunosuppression. We review the literature to evaluate the occurrence of MC in immunosuppressed patients.

## Case Report

A 33-year-old man initially presented for evaluation of severe plaque-type psoriasis associated with pain, erythema, and swelling of the joints of the hands of 10 years' duration. He was started on methotrexate 5 mg weekly and topical corticosteroids but was unable to tolerate methotrexate due to headaches. He also had difficulty

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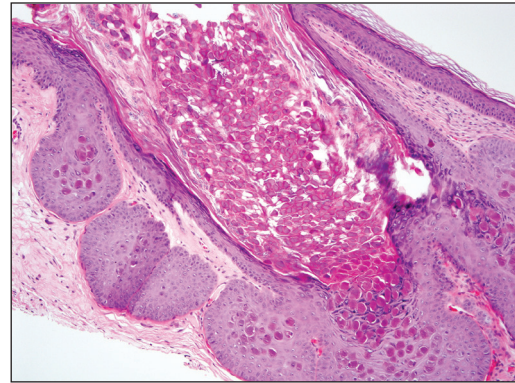
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affording topical medications and adjunctive phototherapy. The patient was sporadically seen in follow-up with persistence of psoriatic plaques involving up to 60% body surface area (BSA) with the only treatment consisting of occasional topical steroids. Five years later, the patient was restarted on methotrexate 5 to 7.5 mg weekly, which resulted in moderate improvement. However, because of persistent elevation of liver enzymes, this treatment was stopped. Several months later he was evaluated for treatment with a biologic agent, and after a negative tuberculin skin test, he began treatment with etanercept 50 mg subcutaneous injection twice weekly, which provided notable improvement and allowed for reduction of dose frequency to once weekly.

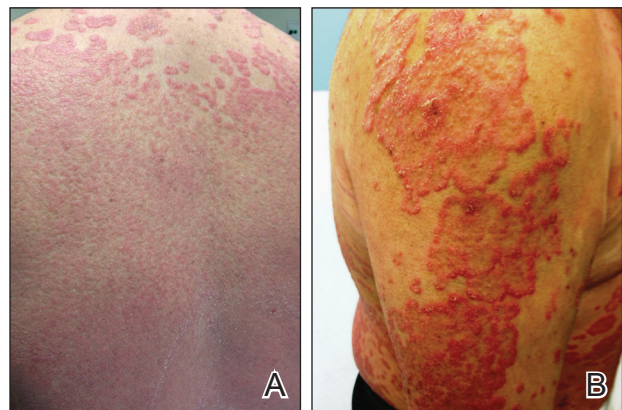
At follow-up 1 year later, the patient had continued improvement of psoriasis with approximately 30% BSA on a treatment regimen of etanercept 50 mg weekly injection and topical corticosteroids. However, on physical examination, there were multiple small semitranslucent papules with telangiectases on the chest and upper back (Figure 1). Biopsy of a representative papule on the chest revealed MC (Figure 2). The patient was subsequently advised to stop etanercept and to return immediately to the clinic for HIV testing. He returned for follow-up 3 months later with pronounced worsening of disease and a new onset of blurred vision of the right eye. Cutaneous examination revealed numerous large erythematous plaques with superficial scale and cerebriform surface on the chest, back, abdomen, and upper and lower extremities involving 80% BSA (Figure 3). Biopsy of a plaque demonstrated psoriasiform dermatitis with neutrophils and parakeratosis consistent with psoriasis. Extensive blood work was notable for reactive HIV antibody and lymphopenia, CD4 lymphocyte count of 60 cells/mm<sup>3</sup>, and an HIV viral load of 247,000 copies/mL, meeting diagnostic criteria for AIDS. Additionally, ophthalmologic evaluation revealed toxoplasma retinitis. Upon initiation of highly active antiretroviral therapy (HAART) and continued use of topical



**FIGURE 1.** Molluscum contagiosum and psoriasis with multiple erythematous papules and plaques scattered on the chest.



**FIGURE 2.** Molluscum contagiosum histopathology revealed epidermal hyperplasia with hypergranulosis and central crater filled with molluscum bodies, with intracytoplasmic inclusions displacing keratohyalin granules and keratinocyte nuclei (H&E, original magnification  $\times 100$ ).



**FIGURE 3.** Psoriasis eruption of numerous confluent erythematous plaques with superficial scale and cerebriform surface on the back (A) and upper arm (B).

corticosteroids, the patient experienced notable improvement of disease severity with approximately 20% BSA.

### Comment

Molluscum contagiosum is a common skin infection. Among patients with HIV and other types of impaired cellular immunity, the prevalence of MC is estimated to be as high as 20%.<sup>3</sup> The MC poxvirus survives and proliferates within the epidermis by interfering with tumor necrosis factor–induced apoptosis of virally infected cells; therefore, intact cell-mediated immunity is an important component of prevention and clearance of poxvirus infections. In immunocompromised patients, the presentation of MC varies widely, and the disease is often difficult to eradicate. This review will highlight the prevalence, presentation, and treatment of MC in the context of immunosuppressed states.

**HIV/AIDS**—Molluscum contagiosum in HIV-positive patients was first recognized in 1983,<sup>2</sup> and its prevalence is estimated to range from 5% to 18% in AIDS patients.<sup>3</sup> Molluscum contagiosum is a clinical sign of HIV progression, and its incidence appears to increase with reduced

immune function (ie, a CD4 cell count  $<200/\text{mm}^3$ ).<sup>3</sup> In a study of 456 patients with HIV-associated skin disorders, the majority of patients with MC had notable immunosuppression with a median survival time of 12 months. Thus, MC was not an independent prognostic marker but a clinical indicator of markedly reduced immune status.<sup>4</sup>

Molluscum contagiosum is transmitted in both sexual and nonsexual patterns in HIV-positive individuals, with the distribution of the latter involving primarily the face and neck. Although it may present with typical umbilicated papules, MC has a wide range of atypical clinical presentations in patients with AIDS that can make it difficult to diagnose. Complicated cases of eyelid MC have been reported in advanced HIV in both adults and children, resulting in obstruction of vision due to large lesions (up to 2 cm) or hundreds of confluent lesions.<sup>5</sup> Giant MC, which appears as large exophytic nodules, is another presentation that has been frequently described in patients with advanced HIV. In these patients, the lesions often are too voluminous for conservative therapy and require excision.<sup>6</sup> Atypical MC lesions also can resemble other dermatologic conditions, including condyloma acuminatum,<sup>7</sup> nevus sebaceous of Jadassohn, ecthyma,<sup>8</sup> and cutaneous horns,<sup>9,10</sup> as well as other bacterial and fungal infections in HIV-positive patients, such as cutaneous *Cryptococcus neoformans*,<sup>11,12</sup> disseminated histoplasmosis,<sup>13</sup> and infections caused by *Penicillium marneffeii*<sup>14</sup> and *Bartonella henselae*.<sup>15</sup> In most cases of MC in HIV-positive patients, diagnosis is dependent on the examination of biopsy specimens, which maintain the same histopathologic features regardless of immune status.

The management of MC in patients with HIV/AIDS is difficult. Molluscum contagiosum has shown no evidence of spontaneous resolution in patients with HIV, and treatment with one modality is often insufficient. Treatment is most successful when a combination approach is utilized with destructive procedures (eg, curettage, cryosurgery) and adjunctive agents (eg, retinoids, cantharidin, trichloroacetic acid). Imiquimod and cidofovir have been used off label for MC in AIDS patients.<sup>16</sup> Imiquimod, which is used to treat genital warts, another cutaneous viral infection seen in patients with HIV, has demonstrated efficacy in treating MC.<sup>16</sup> In a randomized controlled trial comparing imiquimod cream 5% to cryotherapy for MC in healthy children, imiquimod was slow acting but better suited than cryotherapy for patients with eruptions of many small lesions.<sup>17</sup> For HIV patients, numerous reports have described successful treatment of disseminated or recalcitrant MC with topical imiquimod.<sup>18-20</sup> Cidofovir, an antiviral used to treat cytomegalovirus retinitis in patients with AIDS, is a promising antiviral agent against the poxvirus family. In a study of viral DNA polymerase genes of MC virus, cidofovir inhibited MC virus DNA polymerase activity.<sup>21</sup> It has been used in both topical (1% to 3%) and intravenous form to successfully treat recalcitrant and exuberant giant MC.<sup>6,22</sup> However, the use of cidofovir is limited by its high costs, especially when compounded into a topical formulation.<sup>23</sup>

From a systemic standpoint, numerous reports have shown that treating the underlying HIV by optimizing HAART is the most important first step in clearing MC.<sup>24-27</sup> However, a special concern regarding the initiation of HAART in patients with MC as well as a markedly impaired immune function is the development of an inflammatory reaction called immune reconstitution inflammatory syndrome (IRIS). This reaction is thought to be a result of immune recovery in severely immunosuppressed patients. During the initial phase of reconstitution when CD4 lymphocyte counts rise and viral load decreases, IRIS occurs due to an inflammatory reaction to microbial and autoimmune antigens, leading to temporary clinical deterioration.<sup>28</sup> The incidence has been reported in up to 25% of patients starting HAART, and 52% to 78% of IRIS cases involve dermatologic manifestations such as varicella-zoster virus, cytomegalovirus infections, genital warts, and MC.<sup>29,30</sup> In a cohort study of 199 patients, 2% of patients developed MC within 6 months of initiating HAART.<sup>31</sup> In a case of exuberant MC lesions after beginning HAART, the lesions spontaneously resolved with the progression of immune reconstitution.<sup>28</sup>

**Malignancies**—Patients with hematologic malignancies such as lymphoma and leukemia comprise another subset of patients at risk for atypical presentations of MC. Molluscum contagiosum has been described in patients with hematologic malignancies such as adult T-cell leukemia/lymphoma, multiple myeloma, chronic myeloid leukemia, acute lymphoblastic leukemia, lymphomatoid papulosis, and non-Hodgkin lymphoma. In a review of MC in children with cancer, 0.5% were diagnosed with MC.<sup>32,33</sup> Reports also have documented eruptive MC in the presence of solid organ cancers, including lung cancer.<sup>34</sup>

In patients with malignancies, the differential diagnosis should include other common dermatologic conditions such as varicella, herpes simplex, papillomas, pyoderma, and cutaneous cryptococcosis, as well as MC. Similar to HIV-positive patients, the lesions of MC described in patients with malignancies do not tend to spontaneously resolve. In a report of a pediatric patient with acute lymphoblastic leukemia, MC presented as an ulcerated lesion without any classic features, requiring biopsy for definitive diagnosis. Only partial resolution was achieved with cryotherapy and crusting of the lesion in an attempt to slow the progression.<sup>35</sup> In a series of 5 children with hematologic malignancies and MC, little improvement was noted after treatment with surgical scraping, liquid nitrogen, and salicylic acid ointment 5%. Similar to patients with HIV, improvement of immune status and function help clear the disease, and patients who reach remission and discontinue chemotherapeutic agents have a higher rate of spontaneous resolution of previously recalcitrant MC lesions.<sup>36</sup>

**Transplant Patients**—Molluscum contagiosum in transplant patients has features similar to patients with HIV/AIDS. In organ transplant recipients, there is an

increased risk for cutaneous disease from iatrogenic immunosuppression or immunosuppression through infectious or neoplastic processes.<sup>37</sup> As in other immunocompromised populations, MC often has an atypical presentation in transplant patients with more extensive involvement and recalcitrant, rapidly recurring lesions.

In a review of 145 pediatric organ transplant recipients, MC was the fourth most common skin infection after *verruca vulgaris*, *tinea versicolor*, and herpes simplex/zoster. Affecting 7% of patients, the majority of patients demonstrated clinically typical lesions; however, the disease was difficult to eradicate if multiple lesions were present.<sup>37</sup> In other reports in adults, fulminant and giant MC have been described after renal and other solid organ transplants.<sup>38,39</sup> *Molluscum contagiosum* also has been reported to mimic other skin diseases in transplant patients including *tinea barbae*<sup>40</sup> and nodular basal cell carcinomas.<sup>41</sup>

The standard treatments are identical to those used in patients with HIV, including ablative methods via liquid nitrogen, electrocautery, cantharidin, trichloroacetic acid, and topical retinoids. Similar to MC in other immunocompromised states, treatment can be difficult and usually requires multiple modalities. For children, imiquimod cream 5% has been recommended due to high clearance rates (up to 92%) and the painless nature of the treatment.<sup>42,43</sup>

*Other Iatrogenic Immunosuppressive States*—Immunosuppression through the use of steroids, chemotherapeutic agents, and biologic drugs often is the result of treatment of various diseases. In patients with psoriasis treated with systemic immunosuppressive agents, there are numerous reports that describe the appearance of eruptive MC in association with methotrexate, cyclosporine, and biologics. Methotrexate acts as an immunosuppressive agent by binding to dihydrofolate reductase, which inhibits DNA synthesis in immunologically competent cells.<sup>44</sup> It also may block host defense mechanisms against MC by suppressing the expression of serum inflammatory cytokines such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and IFN- $\gamma$  and suppressing the activity of TNF- $\alpha$  inducing apoptosis of virus-infected cells. Cyclosporine used in conjunction with methotrexate may exacerbate the insult to the immune system by inhibiting the production of IFN- $\gamma$ .<sup>45</sup> Biologics are an emerging class of drugs that have demonstrated efficacy in moderate to severe psoriasis by inhibiting TNF- $\alpha$  or other inflammatory molecules. Several published reports have described eruptive or atypical MC in patients on biologic medications. In one case, within 2 weeks after initiation of infliximab, a monoclonal antibody against TNF- $\alpha$ , a patient developed an eruption of MC involving the entire body.<sup>46</sup> In another report, an anti-TNF- $\alpha$  agent for rheumatoid arthritis was associated with atypical MC with eyelid lesions.<sup>47</sup>

There are other skin disorders treated with immunosuppressive agents that also have been associated with MC. In a patient with pemphigus vulgaris treated with prednisolone, pimecrolimus, and azathioprine, MC

lesions were observed on the face and within healed pemphigus vulgaris sites.<sup>48</sup> Pimecrolimus and tacrolimus, corticosteroid-sparing agents, suppress cell-mediated immunity and inhibit inflammatory cytokines such as IL-2. The infection resolved with a gradual tapering of immunosuppressive therapy and 10 sessions of cryotherapy.<sup>48</sup> In a case of topical pimecrolimus for pityriasis alba, the patient developed biopsy-proven MC within 2 weeks of initiating treatment in the areas that were treated with tacrolimus.<sup>49</sup>

In nontransplant patients with iatrogenic immunosuppression, MC treatment has not been documented to be as challenging as in patients with inherent immunosuppression. Most patients respond to either withdrawal of the drug alone or to simple ablative treatments such as cryotherapy.<sup>45,46,48</sup> This important difference is most likely due to the presence of an otherwise intact immune system.

## Conclusion

This case describes the appearance of MC in a patient with psoriasis treated with a TNF- $\alpha$  inhibitor who was ultimately diagnosed with AIDS. Although atypical MC infections have been documented in patients with psoriasis undergoing treatment with biologics, it is thought to be more common for MC to occur in more remarkably immunocompromised states such as AIDS. Thus, the persistence and progression of MC in our patient despite discontinuation of etanercept suggested a separate underlying process. Subsequent workup led to the diagnosis of AIDS along with the opportunistic ocular infection of toxoplasmosis retinitis. This clinical sequence consisting of psoriasis treated with a biologic agent, development of MC, and subsequent diagnosis of AIDS is unique and clinically significant to dermatologists. The presentation of psoriasis in patients with HIV can be diverse with different levels of severity and atypical clinical features. In many cases, HIV is known to exacerbate the classic clinical presentation of psoriasis. However, there are other particular presentations of psoriasis in HIV patients that have been observed, which include a predilection for scalp lesions, palmoplantar keratoderma, flexural involvement, and higher levels of immunodeficiency.<sup>50</sup> Although tuberculin skin tests are required prior to initiating biologic therapy due to the potential for disease reactivation, there are no requirements for HIV antibody testing. In cases of severe recalcitrant psoriasis, an HIV test should be ordered during the workup to establish an early diagnosis so that an HIV-positive patient can avoid poor outcomes from either the disease processes, the use of certain therapeutic agents, or both. Furthermore, the benefit of avoiding possible harm to the patient and potential legal action outweighs the cost of performing surveillance HIV testing in this subset of patients. Thus, due to the potential additive immunosuppressive effect of HIV with biologic therapy, providers should always assess for risk factors and consider testing for HIV in all patients before initiating treatment with immunosuppressive agents such as biologics.

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