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Case Report

Multiple Giant Molluscum Contagiosum Arising on Antiretroviral Therapy: A Visible Marker of Unrecognized Immunological Failure in Advanced HIV Disease

Aulia Yasmin[1*], Endra Yustin Ellistasari[1], Ammarilis Murastami[2], Prasetyadi Mawardi[1]

[1]*Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sebelas Maret/Dr. Moewardi General Hospital, Surakarta, Indonesia*

[2]*Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sebelas Maret/Rumah Sakit UNS, Surakarta, Indonesia*

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***Corresponding author:**
Aulia Yasmin
E-mail: a.yasmin_dv@student.uns.ac.id

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ABSTRACT

Background: Molluscum contagiosum is ordinarily self-limiting, but in profound immunosuppression it becomes extensive, giant and atypical. Published reports almost uniformly describe such lesions as revealing previously undiagnosed HIV; lesions arising in a patient already established on antiretroviral therapy are far less often described and carry a more urgent meaning.

Objective: To describe a fatal case of giant molluscum contagiosum arising on antiretroviral therapy, to show that the eruption marked unrecognized immunological failure, and to specify the measurements the dermatological consultation should have triggered.

Case Presentation: A 39-year-old man presented with one year of enlarging papules and nodules on the eyelids, face, neck, hand and penis, the largest 3.5 × 2.5 × 1.5 cm, and 18 months of pruritic hyperpigmented limb papules, after 24 months of fixed-dose efavirenz, lamivudine and tenofovir disoproxil. Dermoscopy, Giemsa cytology and histopathology confirmed molluscum contagiosum; the limb eruption was pruritic papular eruption. CD4 was 31 cells/μL and CD8 1624 cells/μL, a CD4/CD8 ratio of 0.02; syphilis serology was non-reactive. Serial excision and enucleation, with weekly 90% trichloroacetic acid to the penile lesions, cleared the facial disease by month 3; he died at month 7. No viral load, resistance genotype, cryptococcal antigen or tuberculosis screen was performed.

Conclusion: Giant molluscum contagiosum arising after two years of antiretroviral therapy marks therapy that is not working, not merely advanced HIV disease. An audit identified five indicated measurements never obtained. Dermatologists recognizing this eruption should treat the skin and, at the same visit, trigger a viral load and the advanced HIV disease package of care.

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1. Introduction

The skin is the only organ in which the immune status of a person living with human immunodeficiency virus (HIV) can be inspected directly. Cutaneous disease remains one of the most frequent reasons that people living with HIV attend medical services even where antiretroviral therapy (ART) is freely available, and its burden tracks the degree of immunosuppression rather than the calendar era. In a longitudinal cohort of 11,738 adults enrolled in Washington, DC between 2011 and 2023, 49.4% had at least one dermatological diagnosis and infectious dermatoses were the largest category at 41.4% of the cohort; among newly diagnosed participants the incidence of infectious dermatoses fell from 463 to 41 cases per 1000 between 2011 and 2024, and a lower nadir CD4 count remained independently associated with cutaneous malignancy after adjustment.[1] In a cross-sectional study of 328 patients in Antananarivo, 167 (51%) had at least one mucocutaneous lesion; the mean CD4 count was 119 cells/mm^3 in those with cutaneous manifestations against 262 cells/mm^3 in those without, and the count fell as the number of separate dermatoses rose, with a correlation coefficient of −0.39.[2] Among 227 hospitalized patients in Medellín with 433 recorded mucocutaneous manifestations, 64.4% of which were infectious, oral candidiasis was significantly associated with a CD4 count below 100 cells/mm^3.[3] A retrospective

review of 500 patient files in Türkiye included 179 patients with dermatoses, reported at least one dermatosis in 69.3% of patients, and found a significantly lower CD4 T-lymphocyte ratio in those carrying three or more dermatoses.[4] A cross-sectional study of 250 people living with HIV in South Gujarat documented 364 separate dermatoses, between one and four per patient, and grouped them by World Health Organization immunological stage.[5] Across very different settings the same principle holds: the more the skin is involved, and the more atypically it behaves, the lower the CD4 count is likely to be.

Molluscum contagiosum is one of the clearest expressions of that principle. It is caused by molluscum contagiosum virus, a strictly human *Molluscipoxvirus* whose genomic diversity has only recently been resolved; the characterization of 47 novel complete genomes, including the first complete genotype 3 sequence, brought the total of fully sequenced genomes to 66 and defined six phylogenetic subgroups.[6] The virus persists in the epidermis because it carries a dedicated repertoire of immune-evasion proteins. MC160 contains tandem death effector domains and dampens cyclic GMP-AMP synthase and stimulator of interferon genes signalling, blunting type I interferon induction after cytosolic DNA sensing.[7] MC089 independently inhibits activation of interferon regulatory factor 3, so that two of the principal antiviral transcriptional programmes are suppressed at once.[8] In an immunocompetent host these mechanisms buy the virus months of persistence before cell-mediated immunity clears it. In a host whose cell-mediated immunity has collapsed, they buy it years, and the lesions have time to become enormous.

Giant molluscum contagiosum, conventionally defined as a lesion exceeding 1 cm in diameter, is the result. Its determinants have been mapped in large paediatric datasets rather than in adults, and what those datasets show is that the ordinary determinants do not produce giant disease. A cross-sectional study of 615 children found that facial lesions, eyelid lesions included, were significantly less inflamed than non-facial lesions ($P < 0.001$), with no difference in treatment response.[9] A retrospective study of 2,278 children identified concurrent atopic dermatitis in 347 (15.23%) and found that a defective epidermal barrier increased the number of treatment sessions required without altering the duration of treatment.[10] A comorbidity analysis of the paediatric population drawn from a global federated health-records network has mapped the conditions that cluster with the infection.[11] A further analysis of the same 615-child cohort found that lesion number, lesion diameter, inflammation and outcome did not differ between two ethnic groups whose care-seeking behaviour did.[12] None of these datasets contains a lesion of the size described here, because the determinant of size is not the anatomical site, the epidermal barrier or the population, but the competence of the host's cell-mediated immunity.

The eyelid has become the sentinel site for that reason, and it is also the site at which the diagnosis is most often missed. In a twenty-year series of 994 histopathologically proven eyelid lesions, of which 809 (81.4%) were benign, molluscum contagiosum was the commonest infectious lesion at 25 cases, 3.09% of the benign group, yet its clinical diagnostic accuracy was only 40%, the lowest of any benign lesion in that series.[13] In advanced HIV disease the same site produces lesions that are unmistakable and are too often the first evidence of the infection. A 16-year-old Saudi girl presented with an enlarging right upper eyelid lesion obscuring her visual field; excision yielded a mass of 1.9 × 1.5 × 1.2 cm, and investigation showed an HIV viral load of 42,020 copies/mL with a CD4 count of 28 cells/µL and a CD8 count of 921 cells/µL, the eyelid lesion having been the first clinical indicator of her infection.[14] A 49-year-old woman carried an eyelid lesion for five years, was evaluated by an outside dermatologist without being offered an HIV test, and was found on eventual testing to have a CD4 percentage of 4.9% corresponding to fewer than 20 cells/µL with a viral load above 1.25 million copies/mL; the authors of that report state that eyelid molluscum contagiosum in adults usually manifests in advanced HIV with a CD4 count approximately below 85 cells/µL, a figure they draw from earlier literature rather than derive from their own patient.[15] At the extreme, a lesion has been described arising from the corneal limbus itself in an untreated man with acquired immunodeficiency syndrome whose CD4 count was 11 cells/µL.[16]

In adults the mode of acquisition also matters. Genital molluscum contagiosum in adults is sexually transmitted, and a matched case-control analysis of the All of Us Research Program compared 146 adults with molluscum contagiosum against 1460 demographically matched controls and found substantially raised odds of syphilis (odds ratio 16; 95% confidence interval 2.57 to 99.5), HIV (odds ratio 9.54; 95% confidence interval 3.95 to 23.0), condyloma acuminata (odds ratio 13.9; 95% confidence interval 7.36 to 26.2), chlamydia (odds ratio 6.24; 95% confidence interval 2.38 to 16.4) and genital herpes (odds ratio 4.13; 95% confidence interval 1.87 to 9.15).[17] A diagnosis of adult molluscum contagiosum is therefore an indication for a full sexually transmitted infection screen, HIV testing included.

What almost every one of these reports has in common is the direction of the inference: an unusual molluscum lesion leads to a new diagnosis of HIV. The reverse situation, in which giant molluscum contagiosum appears in a patient whose HIV is already known and who has been swallowing antiretroviral tablets daily for years, is described far less often and, where it is described, the antiretroviral history is reported but not interrogated. Two Indonesian patients with giant eyelid molluscum contagiosum and CD4 counts of 31 and 46 cells/µL had been diagnosed in 2012 and 2016 respectively and were both established on antiretroviral therapy at presentation, a fact recorded in the report without being taken as evidence about the therapy itself.[18] Yet the distinction is decisive. In a patient never treated, giant molluscum

contagiosum is a diagnosis waiting to be made and the remedy is to start therapy: a newly diagnosed 48-year-old man with disseminated molluscum contagiosum, Kaposi sarcoma and a CD4 count of 31 cells/μL achieved complete resolution of both eruptions on antiretroviral therapy alone, his count rising to 218 cells/μL by six months; that report expresses both values per cubic millimetre, which is the same volume.[19] In a patient already treated, the identical skin sign at the identical CD4 count means that the treatment is failing, and the remedy is an entirely different set of actions.

The novelty of the present report is threefold. First, it documents multiple giant molluscum contagiosum, including eyelid involvement, that arose de novo twelve months after the start of first-line antiretroviral therapy rather than before it, and shows that the chronology alone reclassifies the lesion from a diagnostic clue into a treatment-failure alarm. Second, it takes the CD8 count that the record already contained but never used, derives a CD4/CD8 ratio of 0.02, and places that value against the published prognostic literature. Third, rather than auditing the disease, it audits the record: each determinant of outcome that the recent primary literature quantifies is checked item by item against what was actually documented, and the omissions are reported and converted into a short, numbered minimum data set. The aim of this study is to describe a fatal case of multiple giant molluscum contagiosum with pruritic papular eruption in a man with advanced HIV disease on antiretroviral therapy, to demonstrate that the cutaneous presentation constituted a visible and actionable marker of unrecognized immunological failure, and to specify the measurements that should have been triggered at the dermatological consultation.

2. Case Presentation

2.1. History

A 39-year-old man attended the dermatology and venereology outpatient clinic with a one-year history of enlarging lumps on the face, neck and penis. The first lesion had appeared on the penis as a solitary, small, skin-coloured papule. It enlarged progressively and further lesions subsequently developed on the face, the eyelids, the neck and the interdigital web of the right hand. The lesions were occasionally mildly itchy and were never painful. The patient had attempted to remove several of them himself by squeezing them between his fingers, which expressed a white material but was followed by neither resolution nor arrest of spread. Separately, and eighteen months before presentation, he had noticed dark macules and papules on both hands and both feet, intermittently pruritic, which had persisted since.

He denied any previous episode of the same complaint, any food or drug allergy, and any systemic disease such as diabetes mellitus. He had been diagnosed with HIV two years earlier and had since been taking a fixed-dose combination of efavirenz 600 mg, lamivudine 300 mg and tenofovir disoproxil 300 mg daily, without interruption by his account. There was no family history of a similar complaint. He had been circumcised at the age of 10 years. His marital status was divorced. First sexual intercourse was at 25 years of age, with a commercial sex worker. He reported 20 lifetime sexual partners, including his former wife and commercial sex workers; his orientation was heterosexual and contact was genito-genital and genito-oral. The last sexual contact had been two years earlier, with a commercial sex worker, without a condom. The sexually transmitted infection history of his partners was unknown.

2.2. Physical examination

General condition was mildly ill with a fully alert level of consciousness. Blood pressure was 115/56 mmHg, pulse rate 91 beats per minute, respiratory rate 20 breaths per minute and axillary temperature 36.5 °C. Body mass index was 25 kg/m^2, recorded in the source notes as normal weight; by the World Health Organization Asia-Pacific classification this value falls in the obese class I band, and the discrepancy is declared here rather than silently corrected. The absence of wasting is itself informative and is discussed below.

Dermatovenereological examination of the facial region, both eyelids, the anterior and posterior neck, the right hand and the penis showed multiple papules and nodules, the largest measuring 3.5 × 2.5 × 1.5 cm, skin-coloured, pearly white, dome-shaped and bearing a central umbilication. Several of the larger lesions were eroded and crusted, as the temple and cheek lesions of Figure 1A show, and confluent nodules ran along the anterior and posterior neck in Figure 1B and Figure 1C; the periocular nodules themselves lie beneath the redaction bar in every frontal panel. On both upper and lower limbs there were multiple hyperpigmented macules, papules and patches, discrete and in places confluent. The full distribution is shown in Figure 1, and the complete set of clinical and laboratory findings, with abnormal values highlighted in red, is set out in Table 1.

2.3. Investigations

The three confirmatory investigations listed in the lower section of Table 1 were performed: dermoscopy, Giemsa staining of expressed lesional material and skin biopsy. As shown in Figure 2, dermoscopy of a lesion demonstrated roundish and polylobular white-yellow structures with a central umbilication; the source record additionally documented crown vessels at the lesional periphery and radially arranged vessels, and the reader should note that vascular structures are not resolvable at the magnification of the archived captures reproduced here. The distribution recorded in Figure 1 was photographed at the same visit. Panel C of Figure 2 shows that Giemsa staining of expressed material yielded dense clusters of large ovoid molluscum bodies. Biopsy of skin from the left brachial region showed epidermal hyperplasia with a crater-like architecture and the intracytoplasmic inclusions known as Henderson-Patterson bodies, reproduced in panels D and E of Figure 2, consistent with molluscum contagiosum. The biopsy site requires comment: the left arm is listed in the examination record under the pruritic papular eruption and not among the molluscum

sites. The discrepancy is reported here exactly as it stands in the source, and may reflect either an unrecorded molluscum lesion at that site or an error of site in the record; it does not affect the diagnosis, which the dermoscopic and cytological findings support independently. Taken together these three techniques excluded the alternatives listed in Table 2.

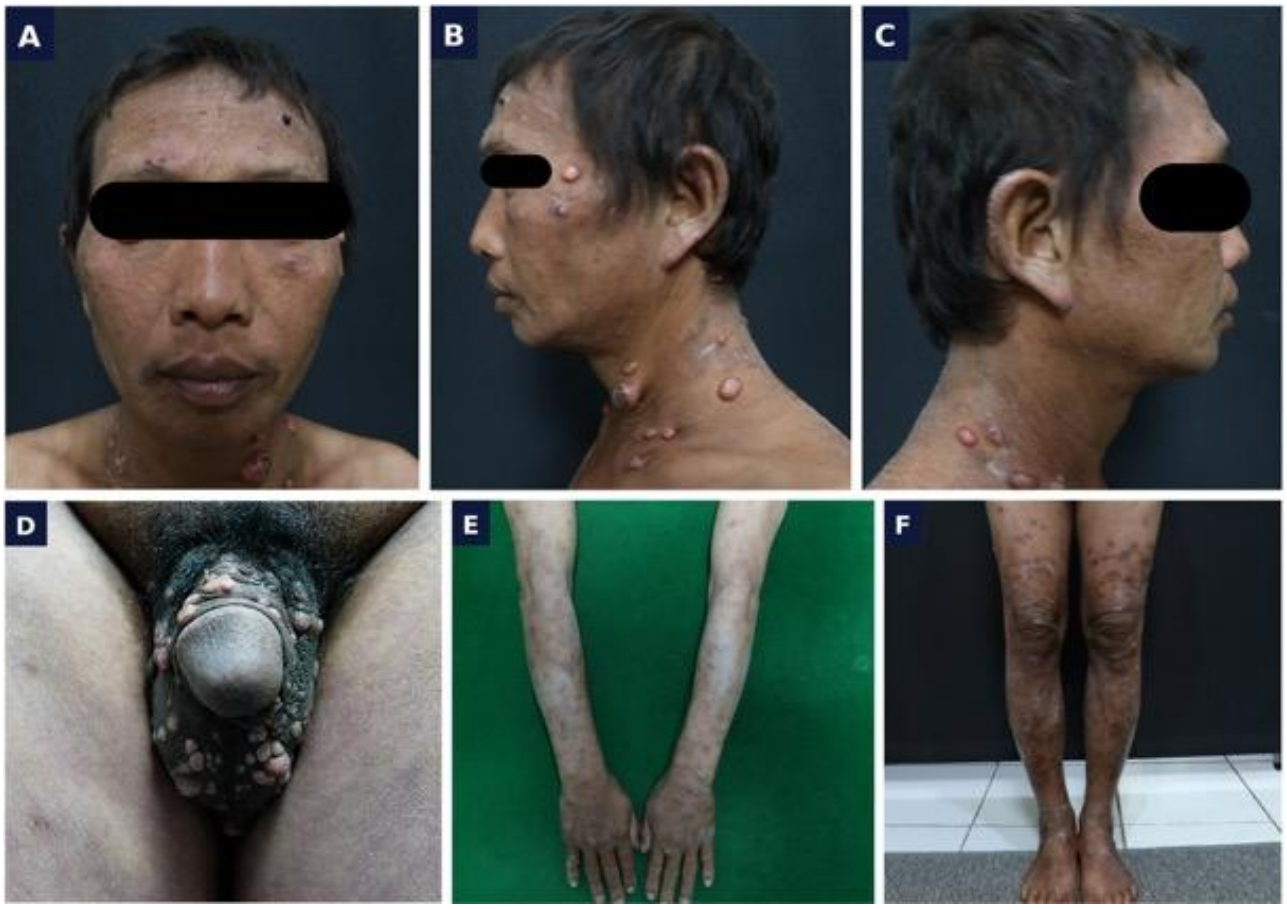

Figure 1. Cutaneous findings at presentation. **(A)** Frontal view showing multiple skin-coloured to pearly-white dome-shaped papules and nodules on the forehead, temples, both eyelids, cheeks, anterior neck and upper chest, several of them eroded and crusted; the periocular nodules lie beneath the redaction bar. **(B, C)** Lateral views showing confluent nodules along the anterior and posterior neck, several of them eroded and crusted. **(D)** Numerous umbilicated papules and nodules of the penile shaft and adjacent pubic skin, the site at which the first lesion appeared. **(E, F)** Multiple discrete and partly confluent hyperpigmented macules, papules and patches of the upper and lower limbs, corresponding to pruritic papular eruption. The ocular region is masked in all facial panels to protect patient identity.

Table 1. Clinical, dermatological and laboratory findings at presentation. Values outside the reference range or outside the range expected in a treated patient are shown in bold red.

Parameter	Finding	Reference range or comment
Demographics, history and exposure		
Age and sex	39 years, male	—
Time since HIV diagnosis	24 months	Diagnosed 2 years before this presentation
Antiretroviral regimen	Efavirenz 600 mg / lamivudine 300 mg / tenofovir disoproxil 300 mg, fixed dose, daily	Taken continuously for 24 months by the patient's own account
Adherence assessment	**Not documented**	Patient report only; no pill count, no pharmacy refill record
Age at first intercourse	25 years	—
Lifetime sexual partners	20, including commercial sex workers	Condomless; last contact 2 years before presentation
Circumcision	Age 10 years	—

Parameter	Finding	Reference range or comment
Vital signs and anthropometry		
Blood pressure	115/56 mmHg	Pulse pressure 59 mmHg
Pulse rate	91 beats/min	60–100 beats/min
Respiratory rate	20 breaths/min	12–20 breaths/min
Axillary temperature	36.5 °C	36.0–37.2 °C
Body mass index	**25 kg/m²**	Recorded as normal weight in the source notes; obese class I by the WHO Asia-Pacific classification*
Dermatological examination		
Sites involved	Face, both eyelids, anterior and posterior neck, right hand, penis‡	Adult eyelid involvement is a recognized marker of advanced HIV disease
Lesion morphology	Skin-coloured to pearly-white dome-shaped papules and nodules with central umbilication	Several periocular nodules eroded and crusted
Largest lesion	**3.5 × 2.5 × 1.5 cm**	Giant molluscum contagiosum is defined as >1 cm; this lesion is 3.5 times that threshold
Limb eruption	Multiple discrete and confluent hyperpigmented macules, papules and patches	Consistent with pruritic papular eruption
Laboratory investigations		
CD4 T-lymphocyte count	**31 cells/µL**	500–1500 cells/µL; <200 defines advanced HIV disease; <100 triggers cryptococcal antigen screening
CD8 T-lymphocyte count	**1624 cells/µL**	200–900 cells/µL
CD4/CD8 ratio (derived)	**0.02**	≥1.0 normal; <0.40 associated with excess mortality. Not calculated at the time†
VDRL	Non-reactive	Non-reactive
TPHA	Non-reactive	Non-reactive
Dermoscopy	Roundish and polylobular structures, central umbilication	Supports molluscum contagiosum
Giemsa cytology	Molluscum bodies present	Supports molluscum contagiosum
Histopathology	Epidermal hyperplasia, crater-like architecture, Henderson-Patterson bodies	Diagnostic of molluscum contagiosum
HIV-1 RNA viral load	**Not performed**	Required to separate virological failure from immunological non-response
Resistance genotype	**Not performed**	Indicated if viral load >1000 copies/mL
Serum cryptococcal antigen	**Not performed**	Recommended at CD4 <100 cells/µL
Tuberculosis screen	**Not documented**	Component of the advanced HIV disease package of care

Notes: ** The discrepancy between the source record and the WHO Asia-Pacific classification is reported here rather than silently corrected. † Derived by the authors from the CD4 and CD8 counts already recorded. ‡ The diagnostic biopsy was taken from the left brachial region, which the examination record lists under the pruritic papular eruption rather than among the molluscum sites; the discrepancy is reported in section 2.3 as it stands in the source. TPHA, Treponema pallidum haemagglutination assay; VDRL, Venereal Disease Research Laboratory; WHO, World Health Organization.*

Screening for syphilis with the Venereal Disease Research Laboratory test and the *Treponema pallidum* haemagglutination assay was non-reactive on both. Lymphocyte subset analysis returned a CD4 count of 31 cells/µL and a CD8 count of 1624 cells/µL. The derived CD4/CD8 ratio, which was not calculated at the time, is 0.02. Figure 3 places all three values against the reference intervals and the operational thresholds that ought to have been triggered.

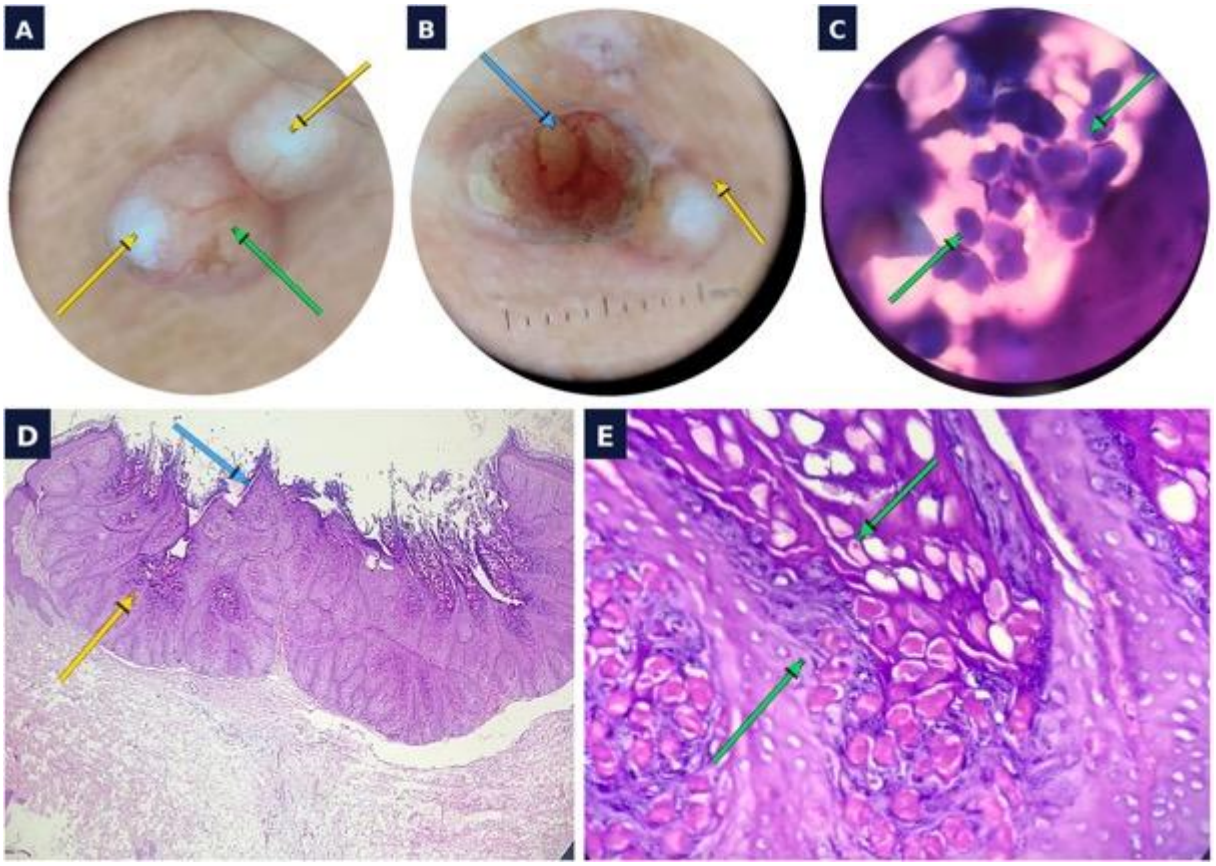

Figure 2. Diagnostic confirmation. **(A, B)** Dermoscopy showing roundish and polylobular white-yellow amorphous structures (yellow arrows), a central umbilication (green arrow) and, in a larger lesion, an eroded and crusted central crater (blue arrow); the millimetre scale of the dermatoscope is visible in panel B. **(C)** Giemsa-stained smear of expressed lesional material showing dense clusters of large ovoid molluscum bodies (green arrows). **(D)** Low-power haematoxylin and eosin section from the left brachial region showing epidermal hyperplasia with a crater-like surface invagination (blue arrow) and endophytic lobules extending into the dermis (yellow arrow). **(E)** High-power view showing the eosinophilic intracytoplasmic Henderson-Patterson bodies (green arrows).

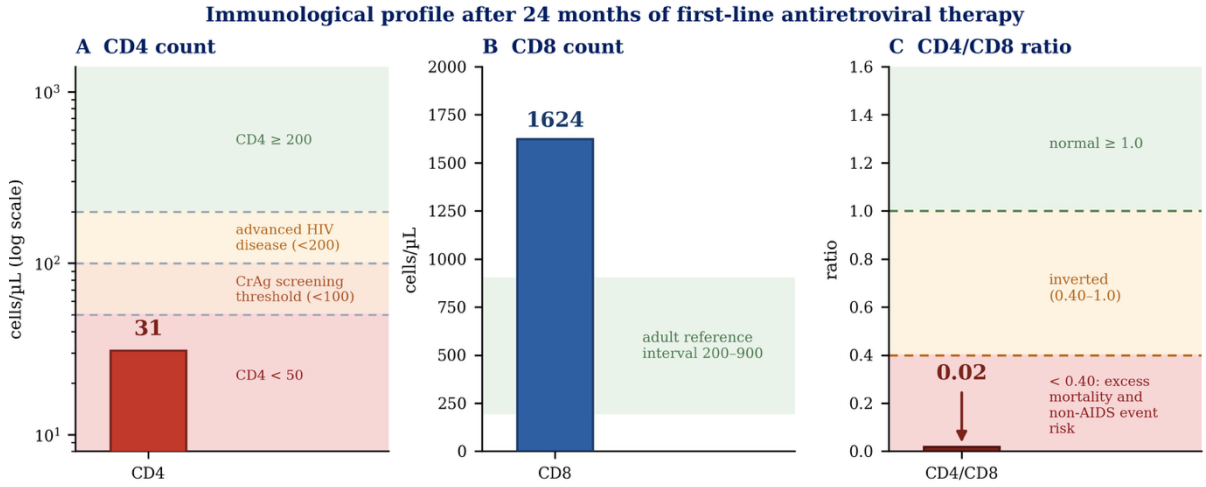

Figure 3. Immunological profile after 24 months of first-line antiretroviral therapy. **(A)** CD4 count of 31 cells/µL plotted on a logarithmic axis against the thresholds that define advanced HIV disease (below 200 cells/µL), that trigger cryptococcal antigen screening (below 100 cells/µL) and that mark the lowest band shown (below 50 cells/µL). **(B)** CD8 count of 1624 cells/µL against the adult reference interval, showing marked expansion rather than recovery. **(C)** The derived CD4/CD8 ratio of 0.02, an order of magnitude below the 0.40 value at which excess mortality and non-AIDS event risk are described in cohort studies. The ratio was obtainable at no additional cost from measurements already performed but was not calculated at the time.

2.4. Diagnosis

On the basis of the history, the physical examination and the investigations, the patient was diagnosed with multiple giant molluscum contagiosum in association with HIV infection, together with pruritic papular eruption. Because the largest lesion measured 3.5 cm in its longest axis and several others exceeded 1 cm, as recorded in Table 1, the case satisfies the conventional definition of giant molluscum contagiosum several times over. The differential considered and excluded at this point is set out in Table 2.

2.5. Management and clinical course

Non-pharmacological management consisted of counselling on the importance of avoiding multiple sexual partners and of condom use. Pharmacological and procedural management comprised serial excision and enucleation of the molluscum lesions of the face and neck; weekly application of 90% trichloroacetic acid to the penile lesions; oral zinc 20 mg three times daily; desoximetasone 0.25% cream twice daily to the pruritic lesions of the hands and feet; and urea 10% cream twice daily to dry areas. The patient remained under shared care with the voluntary counselling and testing service, continued his antiretroviral regimen unchanged, and received co-trimoxazole prophylaxis at the standard adult prophylactic dose of 960 mg once daily. Review was scheduled every two weeks for six months.

The cutaneous response was good. By month 3 the molluscum lesions of the face had resolved completely, including the periocular nodules; Figure 4 shows the before-and-after comparison. At month 7, however, the patient's condition deteriorated and he died. The cause of death is not recorded in the source material, no autopsy was performed, and no terminal opportunistic-infection screen was documented. The full sequence of events, from first sexual exposure to death, is detailed in Figure 5.

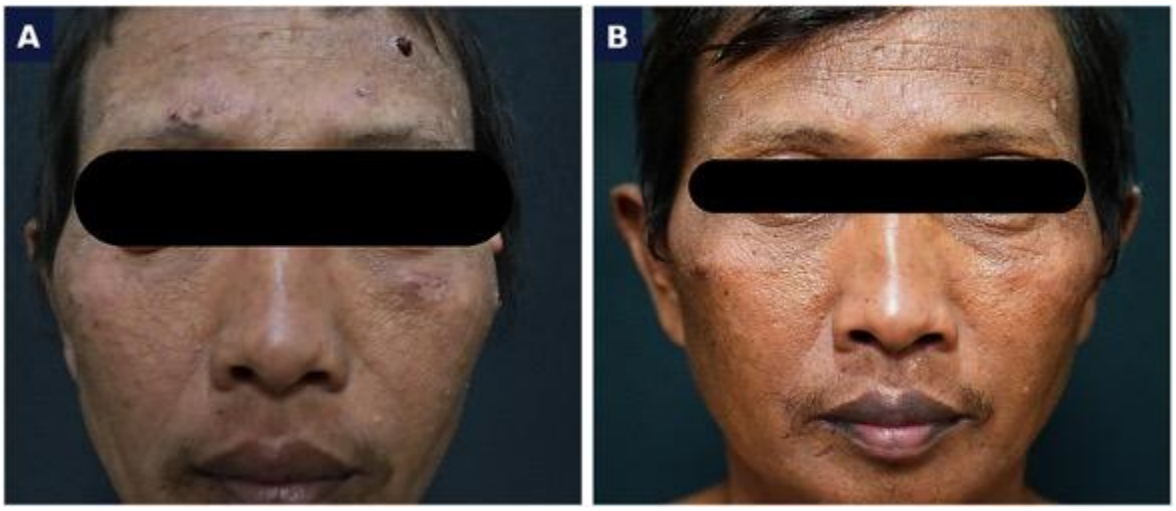

Figure 4. Treatment response of the facial disease. **(A)** At presentation, with multiple papules and nodules on the forehead, temples and cheeks; the giant periocular nodule lies beneath the redaction bar. **(B)** At month 3, after serial excision and enucleation, showing complete clearance of the periocular and facial lesions with residual post-inflammatory change only. The cutaneous response was excellent; the patient nonetheless deteriorated and died at month 7.

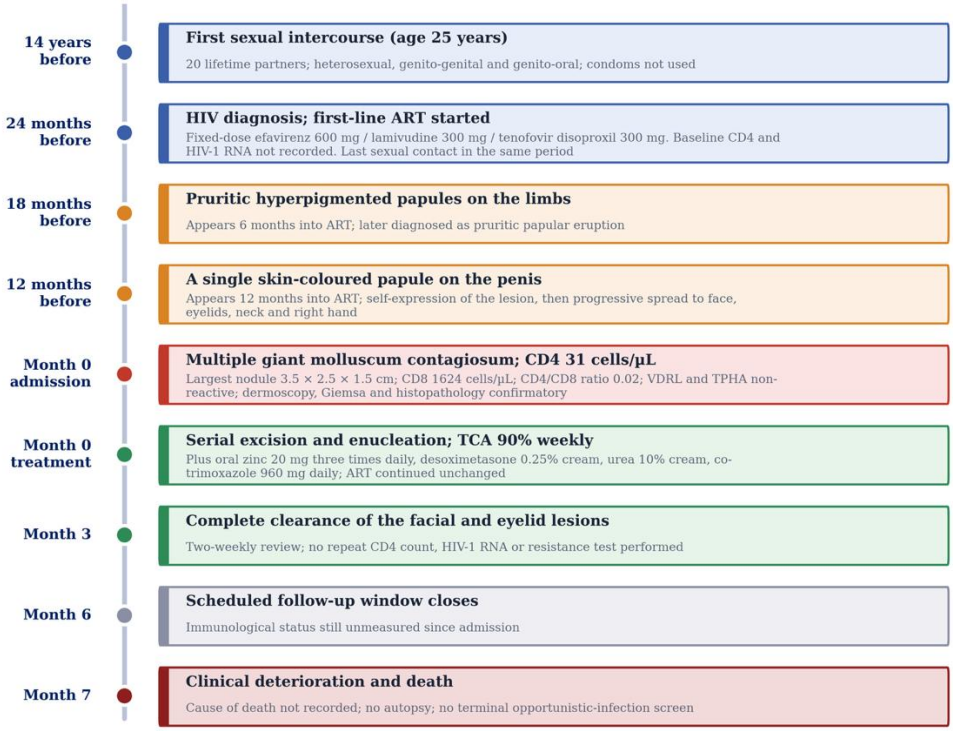

Figure 5. Clinical timeline from first sexual exposure to death. Both cutaneous eruptions arose after antiretroviral therapy had begun, the pruritic papular eruption at six months and the first molluscum lesion at twelve months. The CD4 count obtained at presentation was the only immunological measurement in the record and was never repeated. ART, antiretroviral therapy; TCA, trichloroacetic acid; TPHA, *Treponema pallidum* haemagglutination assay; VDRL, Venereal Disease Research Laboratory.

2.6. Reconstruction of the immunological trajectory

Four features of the chronology deserve to be stated explicitly, because they are visible only when the dermatological history and the antiretroviral history are laid against one another. First, antiretroviral therapy was started 24 months before presentation. Second, the pruritic papular eruption appeared 18 months before presentation, that is, six months into therapy. Third, the first molluscum lesion appeared 12 months before presentation, that is, twelve months into therapy. Both eruptions therefore arose on treatment, not before it. Fourth, after 24 months of therapy the CD4 count stood at 31 cells/μL. No baseline CD4 count, no HIV-1 RNA measurement at any time point, no adherence assessment, no resistance genotype, no serum cryptococcal antigen and no tuberculosis screen appear anywhere in the record, and no World Health Organization clinical stage was assigned at any visit. The single CD4 count obtained at presentation was also the last: it was never repeated during the seven months that followed. Figure 5 sets these events against one another on a single axis.

3. Discussion

3.1. Why the lesions became giant

Molluscum contagiosum virus produces a lesion whose size is governed less by the virus than by what the host is able to do about it. The epidermal lobules enlarge for as long as cell-mediated immunity fails to recognize and clear the infected keratinocytes, and the virus actively engineers that failure. Suppression of cyclic GMP-AMP synthase and stimulator of interferon genes signalling by MC160 removes one arm of the cytosolic DNA-sensing response,[7] while inhibition of interferon regulatory factor 3 activation by MC089 removes another.[8] These mechanisms are constitutive properties of the virus and operate in every host. What differs in advanced HIV disease is that the compensating arm, antigen-specific CD4-dependent clearance, is absent. The consequence is not merely more lesions but qualitatively different lesions: larger, confluent, sited on skin that is not ordinarily involved in adults, and prone to erosion and secondary crusting. Figure 1 illustrates every one of those departures from the ordinary phenotype at once, the crusting being visible on the temple and cheek in Figure 1A and in the dermoscopic view of Figure 2B.

The eyelid deserves separate comment because of the frequency with which it appears in this literature and because of how often it is misread even by the specialty that owns the site: in the twenty-year series of 994 eyelid lesions cited above, the clinical diagnosis of molluscum contagiosum was correct in only 40% of the 25 cases it contained.[13] Giant eyelid lesions have caused visual-field obstruction requiring excision in an adolescent in whom the lesion revealed the HIV infection,[14] and, in an untreated patient with a CD4 count of 11 cells/μL, a nodule arising from the corneal limbus itself.[16] Adult eyelid involvement in particular has been proposed as a marker of advanced disease, with a CD4 count approximately below 85 cells/μL quoted in the literature.[15] The present patient's count of 31 cells/μL, plotted against these thresholds in Figure 3A, sits comfortably below that figure, and falls within the narrow band at or below 46 cells/μL occupied by every comparable published case assembled later in this discussion. The threshold should nonetheless be treated as a descriptive rule of thumb assembled from case material rather than as a validated cut-off, and this is one reason the present report prefers to reason from the ratio and from the treatment history rather than from the absolute count alone.

3.2. The chronology reclassifies the sign

The finding that distinguishes this case from the published series is not the size of the lesions but when they appeared. The pruritic papular eruption emerged six months into antiretroviral therapy and the first molluscum lesion twelve months into it. Neither preceded treatment. This matters, and Figure 5 makes the sequence explicit, because two mechanisms could in principle explain new or worsening cutaneous infection after antiretroviral therapy is started, and they have opposite implications.

The first is immune reconstitution inflammatory syndrome, in which returning immunity unmasks or inflames a pre-existing infection. Molluscum contagiosum can behave this way, and a severe case has been described in which the eruption worsened despite immune reconstitution and required surgical and cytodestructive intervention.[20] Immune reconstitution, however, is by definition accompanied by a rising CD4 count. The present patient's CD4 count after 24 months of therapy was 31 cells/μL, and there is nothing in the record to suggest it had ever been higher. The timing is against it as well: unmasking and paradoxical reactions of this kind characteristically declare themselves within weeks to a few months of starting therapy, whereas the first molluscum lesion here appeared a full twelve months in and continued to progress for a further twelve. Immune reconstitution inflammatory syndrome therefore cannot account for the eruption on either ground.

The second is that the therapy was not working. Here the natural experiment supplied by the literature is unusually clean. A newly diagnosed man with a CD4 count of 31 cells/μL, disseminated molluscum contagiosum and Kaposi sarcoma was started on lamivudine, tenofovir and dolutegravir and required no other intervention: both eruptions resolved completely and the count rose to 218 cells/μL within six months.[19] The starting CD4 count in that patient was identical to the present patient's. The difference lay entirely in whether the antiretroviral regimen was actually suppressing the virus. Where it was, the skin healed as an epiphenomenon of immune recovery. Where it was not, as here, the skin lesions could be excised one by one while the underlying process continued unchecked, which is precisely the course this patient followed: complete clearance of the facial lesions by month 3, shown in Figure 4, and death by month 7. The published cases divide into two groups along exactly this axis.

The mode of spread is worth stating plainly, because it was avoidable. The patient repeatedly expressed the lesions between his fingers, releasing the viral core onto adjacent skin and onto his hands, and the distribution that followed, from an initial penile lesion to the right interdigital web and then to the face and neck, is the distribution that autoinoculation produces. Counselling against manipulation, and a covering dressing over accessible lesions, are cheap interventions that belong in the first consultation at which the diagnosis is made, alongside advice on avoiding skin-to-skin and sexual transmission to others.

A separate observation reinforces the diagnostic value of the eruption itself. The body mass index of 25 kg/m^2 is not the habitus of classical acquired immunodeficiency syndrome. A clinician relying on the gestalt of a wasted patient would have been reassured, and the reassurance would have been false. In a patient whose weight is preserved, the skin may be the only visible evidence that the immune system has failed, which raises rather than lowers the diagnostic value of the eruption.

3.3. The CD8 count the record already contained

The laboratory returned both a CD4 and a CD8 count, and the record used only the first. Dividing one by the other, 31 divided by 1624, yields 0.019, reported throughout as 0.02, against a normal adult value of at least 1.0; the derivation is recorded in the laboratory section of Table 1 and displayed in Figure 3C. The ratio is not a redundant restatement of the CD4 count. It integrates the loss of CD4 cells with the expansion of CD8 cells, and a CD8 count of 1624 cells/µL is itself substantially above the usual adult reference interval; that expansion, plotted against the adult reference interval in Figure 3B, is a marker of persistent antigenic stimulation and immune activation rather than of recovery.

The prognostic literature on this ratio is now substantial. A group-based multi-trajectory analysis of 14,718 adults followed for a median of 55 months after starting antiretroviral therapy resolved four recovery patterns: 32.5% in a group defined by a low CD4 count with CD4/CD8 inversion, 25.9% in a group with a high CD8 count and inversion, 27.2% in a group with slow CD4 recovery and inversion, and 14.4% in a group with rapid CD4 increase and a normal ratio. Taking the high-CD8-with-inversion group as the reference, the low-CD4-with-inversion group carried an adjusted all-cause mortality hazard ratio of 3.28 (95% confidence interval 2.33 to 4.60) and an adjusted AIDS-related mortality hazard ratio of 5.92 (95% confidence interval 3.26 to 10.77).[21] A separate 15-year cohort of 14,293 people living with HIV identified three ratio trajectories, of which the largest, a baseline-low class comprising 8,212 patients (57.45%), served as the reference; the two classes with better trajectories had adjusted all-cause mortality hazard ratios of 0.53 (95% confidence interval 0.38 to 0.75) and 0.35 (95% confidence interval 0.14 to 0.86), with crude mortality falling from 5.26 to 2.46 to 1.28 deaths per 1000 person-years across the three classes.[22] Risk is not confined to AIDS-defining events. Among 83,893 people with HIV contributing 744,415 person-years and 5,628 incident cancers, a six-month-lagged CD4/CD8 ratio of 0.3 compared with 0.8 was associated with a 24% higher risk of any incident cancer, adjusted for CD4 count, HIV RNA and other covariates (adjusted hazard ratio 1.24; 95% confidence interval 1.14 to 1.35); the investigators note explicitly that because the model adjusted for CD4 count, the association reflects the contribution of the higher CD8 count.[23] Immunological non-response is likewise associated with non-AIDS events in a Taiwanese multicentre cohort of 289 patients of whom 44 were non-responders.[24]

None of these studies enrolled a patient with a ratio of 0.02, which lies far below the range in which the published hazard ratios were estimated. The correct inference is therefore qualitative rather than quantitative: the value is not merely low but is an outlier below the distributions from which the risk estimates derive, and it should have been read as a demand for immediate investigation. Figure 3C plots the result. It cost nothing to calculate; the numbers were already on the page, which is why the care-gap audit below classes the CD8 count as obtained but not interpreted rather than as missing.

3.4. What the numbers implied and what was never tested

A CD4 count of 31 cells/µL after 24 months of continuous first-line therapy admits of three explanations, and the record allows none of them to be excluded. The first is poor adherence despite the patient's account. The second is virological failure with acquired drug resistance. The third is genuine immunological non-response despite virological suppression. A fourth possibility, that the count had risen substantially from an even lower starting value and that the response was therefore partial rather than absent, cannot be assessed at all, because no baseline CD4 count was recorded when therapy began and no CD4 gain can be computed.

Immunological non-response is well described and is not rare. In a Chinese national cohort of 3,900 patients grouped by CD4 count 24 months after starting therapy, 2,309 (59.2%) were immunological responders, 1,206 (30.9%) were incomplete responders and 385 (9.9%) were non-responders, with male sex (adjusted odds ratio 2.07; 95% confidence interval 1.39 to 3.09) and increasing age among the associated factors.[25] Across two international cohorts of virally suppressed patients, non-response prevalence was 10.8% and 25.8%, and a higher CD4 nadir was protective, with adjusted odds ratios of 0.34 and 0.48 per 100 cells/µL.[26] The most directly relevant data come from Indonesia itself: among 382 analysable virologically suppressed adults on therapy at two hospitals in Surabaya, a baseline CD4 count below 200 cells/µL strongly predicted non-response, with adjusted odds ratios of 5.60 (95% confidence interval 2.95 to 10.62) and 4.46 (95% confidence interval 2.39 to 8.29) depending on the definition applied.[27] Machine-learning approaches to predicting non-response are being developed,[28] and the

choice of anchor drug influences the speed of CD4 recovery in advanced disease: among 1,349 people with advanced HIV starting therapy, the likelihood of reaching a CD4 count of at least 200 cells/μL was lower with dolutegravir-containing regimens than with bictegravir, emtricitabine and tenofovir alafenamide (hazard ratio 0.82; 95% confidence interval 0.69 to 0.98).[29] Zinc supplementation, which this patient received, has been formally tested in exactly this population; a randomized double-blind study in patients with immunovirological discordance took as its premise that between 15% and 18% of patients starting therapy fail to achieve immune recovery despite complete virological suppression.[30]

Crucially, however, immunological non-response is a diagnosis of exclusion that can only be made once virological suppression has been demonstrated. Without an HIV-1 RNA measurement it cannot be distinguished from virological failure, and the regional data make virological failure a serious possibility. In a subanalysis of a randomized trial in rural South Africa, pretreatment drug resistance was detected in 12.9% (25 of 194 sequenced participants) of patients starting efavirenz-based first-line therapy, 19 of whom carried non-nucleoside reverse transcriptase inhibitor resistance, and its presence adversely affected outcomes.[31] In Bandung, West Java, a cross-sectional study of 112 patients (71 on antiretroviral therapy and 41 pretreatment) found non-nucleoside reverse transcriptase inhibitor resistance mutations in 7% of treated and 14.6% of pretreatment patients, with reverse transcriptase gene mutations in 12.7% and 17.1% of the two groups respectively; efavirenz with a tenofovir and lamivudine backbone was the regimen most patients had received, the same combination this patient was taking.[32] Access to the test that would have resolved the question is the recognized weak point of programmes across the region. Among 6,277 patients in the TREAT Asia HIV Observational Database, 3,247 (52%) attended sites without routine viral load monitoring; virological failure occurred in 16% of patients at both routine and non-routine sites, but the adjusted incidence rate ratio for failure at non-routine sites was 2.85 (95% confidence interval 2.27 to 3.59) relative to routine sites, and the median interval from documented failure to switching regimen was six months (interquartile range 2 to 23).[33] Comparable gaps have been documented in eight sub-Saharan African countries[34] and in remote provinces of Vietnam.[35] Resistance to the drug class now replacing efavirenz is not yet a barrier: among 353 integrase sequences from West Africa and Southeast Asia, pretreatment resistance to integrase strand transfer inhibitors was 1.1% (4 of 353), against 17.9% (95% confidence interval 13.9% to 22.3%) for resistance to any drug class, of which non-nucleoside reverse transcriptase inhibitor resistance accounted for 9.7% and nucleoside analogue resistance for 5.3%.[36] Where the transition to dolutegravir has been implemented at scale, viral suppression has risen markedly, from 57.1% in 2014 to 90.3% in 2022 in one population-based Ugandan cohort,[37] and a survey of 175 participating clinics across 35 low- and middle-income countries has mapped how unevenly viral load and resistance testing accompany that transition.[38] Adherence itself is measurable and its determinants are known, including depressive symptoms and food insecurity in a cohort of 501 patients followed for 96 weeks,[39] and clinical and immunological profiles of first-line treatment failure have been characterized in tertiary practice.[40] A high viral load at treatment initiation independently predicts both subsequent virological failure and death: among 7,176 patients in Chongqing, 38.7% began therapy with a viral load of at least 100,000 copies/mL.[41]

Figure 3 displays the problem and the lower rows of Table 1 state it in words: three measurements that were abnormal, and four laboratory tests that were never performed (Table 5 adds the undocumented adherence assessment, giving five omissions in all). The honest summary is that this patient had a syndrome whose differential diagnosis is narrow, whose resolution required a single blood test costing less than the surgical time spent excising his nodules, and that the test was not done. The limitation must be stated before the inference: because no viral load was measured, it is not possible to establish retrospectively whether this patient failed virologically or immunologically. That uncertainty is precisely the finding.

3.5. Advanced HIV disease: a package of care that was not delivered

A CD4 count below 200 cells/μL defines advanced HIV disease, for which the World Health Organization recommends a defined package: tuberculosis diagnostics including sputum Xpert and urine lipoarabinomannan, tuberculosis preventive therapy, serum cryptococcal antigen screening with pre-emptive fluconazole where positive, co-trimoxazole prophylaxis, and rapid initiation or optimization of antiretroviral therapy. Modelling of a Malawian cohort in which 25% of those starting therapy had advanced disease compared 13 increasingly comprehensive strategies and found the full package cost-effective; the same analysis notes that between 20% and 40% of people living with HIV in sub-Saharan Africa present with advanced disease.[42] Implementation with point-of-care CD4 testing during tuberculosis case-finding has been shown to be feasible in Lesotho and South Africa.[43] Risk within this group can be stratified further: among 1,378 Ugandan outpatients with a CD4 count of 200 cells/μL or below who had C-reactive protein measured, 41.6% had a value of at least 10 mg/L, and those patients were more likely to be hospitalized (relative risk 4.2; 95% confidence interval 2.3 to 7.8) or to die (relative risk 9.8; 95% confidence interval 2.9 to 32.8) within 30 days.[44]

Of that package, this patient received co-trimoxazole and nothing else, an omission set out item by item in the audit below. The omission of cryptococcal antigen screening is the most consequential, for two reasons. The first is that the recommendation applies squarely to him. The second is that the yield in antiretroviral-experienced patients is not lower than in the treatment-naive group in whom screening is conventionally performed. In 104 rural Ugandan facilities, 7,210

antiretroviral-experienced patients with viral load non-suppression were eligible for screening but only 830 (11.5%) were screened, of whom 87 (10.5%) were antigen-positive; among treatment-naive patients with a CD4 count below 100 cells/μL, 891 of 937 eligible patients (95.1%) were screened and 123 (13.8%) were positive, a difference in yield of borderline significance (P = .035) against a more than eightfold difference in the probability of being screened at all (P < .001).[45] The pattern of missed opportunity is not confined to Uganda: in an American ambulatory cohort of 2,201 eligible individuals with poor virological control, cryptococcal antigen screening was performed in 2.9%.[46] Even where screening is systematic, the downstream cascade leaks: in a nationally sampled South African cohort, 85,791 of 86,274 eligible patients (99%) were tested and 5,124 (6.0%) were positive, yet among 1,651 patients with retrievable records and no concurrent meningitis only 39% had a documented meningitis symptom review, fluconazole was dispensed to 50%, and only 32% received an adequate daily dose of at least 800 mg.[47]

This matters clinically here and not only administratively. Disseminated cryptococcosis produces umbilicated papules that are indistinguishable from molluscum contagiosum on inspection, and the two conditions occupy the same immunological niche. Cross-sectional screening of 262 asymptomatic outpatients with advanced HIV disease in Kinshasa found serum cryptococcal antigen in 47 of them (18%; 95% confidence interval 14.2 to 24.3), and asymptomatic cryptococcal meningitis was present in 19 of the 38 antigen-positive patients who consented to lumbar puncture (50%).[48] A cohort in Guangzhou found an overall antigen positivity of 5.1%, of whom 94.7% had a baseline CD4 count of 200 cells/μL or below; positivity was 6.4% in antiretroviral-naive and 4.7% in antiretroviral-experienced patients, and within the treated group a shorter time on therapy was independently associated with positivity (adjusted odds ratio 2.53, 95% confidence interval 1.20 to 5.34, for one year or less against more than two years) as was the presence of another opportunistic infection (adjusted odds ratio 2.56, 95% confidence interval 1.41 to 4.63). Those investigators concluded that screening should be extended to every patient with a CD4 count of 200 cells/μL or below regardless of antiretroviral status.[49] That is precisely the recommendation this record fails. The patient died at month 7 of an undocumented cause. Cryptococcal disease cannot be established as that cause and it is not claimed here; what can be established is that a screening test which would have detected one common and treatable explanation was indicated, is cheap, and was not performed.

3.6. Differential diagnosis

Because a solitary inspection cannot distinguish molluscum contagiosum from several conditions that share its morphology in advanced HIV disease, Table 2 sets out the practical differential and the features that separate its members. The essential clinical rule, stated in the footnote to Table 2, is that in a patient with a CD4 count below 100 cells/μL umbilicated papules require tissue or antigen confirmation rather than clinical diagnosis alone, and the confirmation should be sought before, not after, destructive treatment is undertaken. Table 2 therefore pairs each differential entry with the specific test that settles it. The present case followed that rule: dermoscopy, cytology and histopathology were all obtained.

Table 2. Differential diagnosis of umbilicated papules and nodules in an adult with a CD4 count below 100 cells/μL, and the feature that separates each from molluscum contagiosum.

Condition	Clinical and dermoscopic clues	Confirmatory test	Why it matters here
Molluscum contagiosum	Pearly-white dome-shaped papules with central delle; roundish or polylobular white-yellow structures with crown vessels on dermoscopy	Giemsa cytology; histopathology showing Henderson-Patterson bodies	The diagnosis made here, confirmed by three independent techniques
Disseminated cryptococcosis	Umbilicated papules clinically indistinguishable from molluscum contagiosum; often febrile, headache or systemic upset	Serum cryptococcal antigen; India ink; fungal stains on biopsy	**Rapidly fatal if missed; the screening test was not performed**
Disseminated histoplasmosis or talaromycosis	Umbilicated papules with central necrosis; endemic exposure history; hepatosplenomegaly	Fungal culture; tissue histopathology; antigen assays	Endemic in parts of Southeast Asia; excluded only by biopsy
Condyloma acuminatum	Verrucous rather than dome-shaped; dermoscopic overlap with genital molluscum is well described	Clinical, dermoscopy, histopathology	The first lesion here was penile; overlap is a recognized pitfall
Cutaneous Kaposi sarcoma	Violaceous macules, papules and plaques rather than pearly nodules	Histopathology; human herpesvirus 8 staining	Coexists with molluscum contagiosum at similar CD4 counts
Basal cell carcinoma (solitary lesions)	Pearly papule with arborizing telangiectasia; solitary and slowly progressive	Histopathology	Considered for a solitary giant nodule, excluded by multiplicity
Verruca vulgaris	Hyperkeratotic, thrombosed capillaries on dermoscopy, no central umbilication	Clinical; histopathology if atypical	Common co-infection in advanced HIV disease

Notes: *At a CD4 count below 100 cells/μL, umbilicated papules warrant tissue or antigen confirmation rather than clinical diagnosis alone, and confirmation should precede destructive treatment.*

3.7. Diagnostic confirmation in practice

Dermoscopy is the least invasive of the three confirmatory techniques and performs well. Reported features include roundish, polylobular or four-leaved-clover-like white-yellow amorphous structures, with crown vessels arranged at the lesional periphery and radial vessels. Where the morphology is ambiguous, reflectance confocal microscopy evaluated against five clinical mimics of facial papules in children resolves the cyst-like structures of molluscum contagiosum and separates them from milia, keratosis pilaris, verruca plana, seborrhoeic keratosis and juvenile xanthogranuloma by the location and the refractive index of the cystic contents.[50] Where the question is virological rather than morphological, a digital polymerase chain reaction assay now detects molluscum contagiosum virus in clinical samples, assigns it to genotypes 1 to 3 and qualifies it to one of six phylogenetic subgroups.[51] In the present case the archived dermoscopic images reproduced as Figure 2A and Figure 2B demonstrate the roundish and polylobular structures and the central umbilication clearly; the vascular features recorded in the notes are not resolvable in the images available, and this is stated as a limitation of the material rather than as an absence of the finding.

Giemsa staining of expressed lesional material is rapid, requires no laboratory beyond a microscope, and demonstrates molluscum bodies directly; this was the technique that gave the earliest confirmation in the present patient. Histopathology remains definitive, showing epidermal hyperplasia forming a crater filled with the eosinophilic intracytoplasmic inclusions described by Henderson and Patterson, both features visible in Figure 2D and Figure 2E respectively. In advanced HIV disease histopathology carries the additional and arguably more important function of excluding the deep fungal infections that mimic molluscum contagiosum, which is why biopsy should be regarded as routine rather than optional at this CD4 level, and why every fungal entry in Table 2 carries a tissue-based or antigen-based confirmatory test rather than a clinical one.

3.8. Treatment in the setting of profound immunosuppression

No standard therapy exists for molluscum contagiosum in HIV infection, and the randomized evidence that does exist was generated in a different population. The integrated analysis of three randomized controlled trials of berdazimer gel 10.3%, a topical nitric-oxide-releasing agent, enrolled 1,598 patients aged six months and above with 3 to 70 lesions and showed complete clearance at week 12 in 30.0% of those treated compared with 19.8% of those receiving vehicle (odds ratio 1.75; 95% confidence interval 1.38 to 2.23; P < .001).[52] A post hoc analysis of the same three trials separated the 209 patients (13.1%) who also had atopic dermatitis from the 1,389 who did not, and found complete clearance of 35.0% against 27.4% with vehicle in the first group (odds ratio 1.3; 95% confidence interval 0.7 to 2.5) and 29.1% against 18.9% in the second (odds ratio 1.8; 95% confidence interval 1.4 to 2.4).[53] The pivotal phase 3 trial that contributed to both analyses, conducted at 55 mostly dermatological and paediatric clinics, explicitly excluded patients with sexually transmitted molluscum contagiosum and patients with lesions confined to the periocular area,[54] which are the two categories into which the present patient falls. A prospective comparison of curettage against electrodesiccation in 103 paediatric patients with at least 10 lesions, or five on the face, provides useful procedural comparison but again in children.[55] Immunotherapy has been evaluated in an observational study of intralesional measles, mumps and rubella vaccine in 22 patients, in which 18 (81.8%) achieved complete clearance and the remaining 4 (18.2%) a partial response of more than 50%, the single patient with a giant lesion being the only one to develop post-inflammatory hyperpigmentation.[56] Autoinoculation, which likewise induces a cell-mediated response to viral antigen, produced an excellent response, defined in that study as a reduction of more than 90% in the number of lesions rather than as clearance, in 18 of 30 evaluable patients (60%) with more than five genital lesions,[57] and has been compared with 35% trichloroacetic acid in a randomized pilot.[58] The mechanism of both, however, depends on the very cell-mediated immunity that is absent at a CD4 count of 31 cells/µL, and neither should be expected to perform in this setting. The evidence that applies directly to giant lesions in profoundly immunosuppressed adults remains case-based: two patients with CD4 counts of 31 and 46 cells/µL, both already established on antiretroviral therapy, whose giant eyelid lesions improved within four weeks on adjuvant self-applied 20% potassium hydroxide.[18] Destructive treatment of periocular lesions also carries its own hazard: the eyelid margin lies within millimetres of the cornea, and both chemical and physical modalities have been associated with ocular surface injury, which is why the excision and enucleation used here, performed under direct vision, is preferable at that site to a caustic applied by the patient. One further caution belongs with any destructive approach. Inflammation of a molluscum lesion is usually the prelude to its resolution rather than bacterial superinfection: of 57 cultures taken from 51 children with inflamed lesions only 7 (12%) grew a pathogen, yet 36 (71%) received a topical and 32 (63%) a systemic antibiotic, and 47% of 118 responding paediatricians reported never culturing such lesions.[59] In a patient with a CD4 count of 31 cells/µL the balance of that judgement shifts, but the discipline of culturing before treating does not. Every modality named in this section, with the evidence behind it and the question that matters most at a CD4 count of 31 cells/µL — whether its mechanism requires host cell-mediated immunity — is set out in Table 3, which lists each row against that single question.

Table 3. Treatment modalities for molluscum contagiosum, with the evidence available in immunosuppressed adults and the question that matters most at a CD4 count of 31 cells/μL: whether the mechanism requires host cell-mediated immunity.

Modality	Agent or technique, and the evidence for it	Evidence type	Depends on host cell-mediated immunity?
Antiretroviral therapy			
Effective virological suppression	Complete resolution of disseminated molluscum contagiosum and Kaposi sarcoma on therapy alone, with the CD4 count rising from 31 to 218 cells/μL over six months	Case report	Yes — it restores it
Physical and surgical destruction			
Excision and enucleation	Used here for the facial and cervical lesions; preferred at the eyelid margin, where a caustic risks ocular surface injury	Clinical experience and case reports	No
Curettage or electrodesiccation	Compared prospectively in 103 paediatric patients with at least 10 lesions, or five on the face	Prospective comparative study	No
Chemical destruction			
Trichloroacetic acid 90%	Used here weekly for the penile lesions. No randomized trial has tested this concentration in molluscum contagiosum, and the periocular hazard precludes its use at the lid margin	No trial evidence in this indication	No
Potassium hydroxide 20%	Giant eyelid lesions improved within four weeks in two patients with CD4 counts of 31 and 46 cells/μL, both already established on antiretroviral therapy	Case reports	No
Topical antiviral and immunomodulatory			
Berdazimer gel 10.3%	Complete clearance 30.0% against 19.8% with vehicle at week 12 (odds ratio 1.75, 95% CI 1.38–2.23) among 1,598 patients; 35.0% against 27.4% in the 209 with atopic dermatitis and 29.1% against 18.9% in the 1,389 without. The pivotal trial excluded sexually transmitted and periocular-only disease	Integrated and post hoc analyses of three randomized trials	Partly
Intralesional measles, mumps and rubella vaccine	Complete clearance in 18 of 22 patients (81.8%) and a partial response of more than 50% in the remaining 4	Observational study	**Yes — unlikely to work here**
Autoinoculation	Excellent response, defined as more than 90% reduction in lesion number, in 18 of 30 evaluable patients (60%) with more than five genital lesions	Clinical study; randomized pilot versus 35% TCA	**Yes — unlikely to work here**
Adjunctive care			
Culture before treating an inflamed lesion	Only 7 of 57 cultures (12%) from inflamed lesions grew a pathogen, yet 36 of 51 patients (71%) received a topical and 32 (63%) a systemic antibiotic	Retrospective study with clinician survey	Not applicable
Counselling against self-expression	Manipulation releases the viral core onto adjacent skin; covering accessible lesions limits autoinoculation and transmission	Clinical principle	Not applicable

Notes: *CI, confidence interval; TCA, trichloroacetic acid. Destructive treatment clears lesions but does not alter the immunological substrate that allowed them to become giant, which is why the first row of this table is the one that governs the outcome.*

The clearance shown in Figure 4 was achieved entirely by physical and chemical destruction. The final column of Table 3 is the one that governs the choice at this CD4 count, and Table 3 places the two modalities actually used here, excision with enucleation and 90% trichloroacetic acid, in the rows that do not depend on host immunity. The therapeutic principle that emerges is straightforward and was only half applied here. Physical and chemical destruction clears lesions and did so successfully, with the complete facial clearance by month 3 documented in Figure 4. But destruction does not alter the substrate. The definitive treatment for molluscum contagiosum in HIV infection is effective antiretroviral therapy, as the case of complete resolution of both molluscum contagiosum and Kaposi sarcoma on antiretroviral therapy alone demonstrates.[19] In the present patient the antiretroviral regimen was continued unchanged, and it was the one component of management that the clinical picture had specifically called into question. Table 3 lists it in the first row for that reason, and the footnote to Table 3 states the principle explicitly.

3.9. Comparison with published cases

Table 4 places the present case against the published reports of giant or eyelid molluscum contagiosum in HIV infection for which CD4 data and antiretroviral status are retrievable. Table 4 is deliberately divided into two blocks rather than ordered by CD4 count, and two things emerge from that arrangement. The first is that the CD4 counts cluster tightly at or below 46 cells/μL, between 11 and 46 where a point value is reported, which supports the sentinel status of the sign.

The second point, and the reason for the table, is that antiretroviral status splits the reports into two groups with entirely different meanings. The upper block of Table 4 shows what happens when the patient is treatment-naive and the lesion reveals the diagnosis:

starting therapy addresses both the skin and the underlying disease, and outcomes were good in every such report. The lower block of Table 4 shows the opposite situation. Where the patient was already on therapy, as in the two Indonesian cases and the present one, the identical lesion at an identical CD4 count was a statement about the therapy, and in the published reports that statement was recorded without being acted upon. The present case, the last row of Table 4, is to the authors' knowledge the first in which that distinction is made explicit and followed to its clinical conclusion.

Table 4. Published reports of giant or eyelid molluscum contagiosum in HIV infection with retrievable CD4 data, compared with the present case. Antiretroviral status at presentation, not CD4 count, separates the reports into two groups with different clinical meanings.

Report	Patient	Site and size	CD4 (cells/μL)	ART status at presentation	Outcome
Antiretroviral-naive at presentation: the lesion revealed the diagnosis					
Alghamdi et al., 2023	16-year-old female	Right upper eyelid; 1.9 × 1.5 × 1.2 cm	28	Naive; started after diagnosis	Excision; no recurrence at six months
Ortega et al., 2024	49-year-old female	Left upper eyelid margin and face; 3 mm	<20*	Naive; not previously tested	Diagnosed with AIDS at this presentation
Guechchati et al., 2025	48-year-old male	Disseminated, with Kaposi sarcoma	31	Newly diagnosed; HAART started	Complete resolution of both eruptions; CD4 rose to 218 cells/μL at 6 months
Fujita et al., 2022	46-year-old male	Corneal limbus nodule	11	Untreated AIDS	Excised; diagnosis confirmed histologically
Already on antiretroviral therapy at presentation: the lesion was a statement about the therapy					
Achdiat et al., 2021 (case 1)	36-year-old male	Both eyelids; multiple confluent	31	On ART; diagnosed 2012, ART from 2017	Improved within four weeks with 20% KOH; ART status not interrogated
Achdiat et al., 2021 (case 2)	26-year-old female	Left eyelid; multiple papules	46	On ART; diagnosed 2016, taking ARV routinely	Improved within four weeks with 20% KOH; ART status not interrogated
Present case, 2026	39-year-old male	Eyelids, face, neck, hand, penis; 3.5 × 2.5 × 1.5 cm	**31**	**On ART 24 months; lesions arose at month 12**	**Facial clearance at month 3; died at month 7; no viral load ever measured**

Notes: ** Reported as a CD4 percentage of 4.9%, corresponding to fewer than 20 cells/μL; no point value is given in the source. ART, antiretroviral therapy; ARV, antiretroviral; HAART, highly active antiretroviral therapy; KOH, potassium hydroxide.*

3.10. The care gap and a proposed minimum data set

The care gap is detailed in Table 5, which audits this record item by item against the measurements that the recent primary literature identifies as determinants of outcome in a patient with a CD4 count below 200 cells/μL. Table 5 divides the record into what was obtained and used, what was indicated and not obtained, and what is worth adding where available, and lists against each entry the indication that existed and what the measurement would have changed. Five items fell into the middle block and one further item into the third. Rather than leave the audit as a list of criticisms, Table 5 converts it into a numbered minimum data set that a dermatologist can order at the consultation at which giant molluscum contagiosum is diagnosed in a patient known to have HIV; the numbering of the five items below follows the numbering of the table.

Table 5. Care-gap audit of the present record against the measurements that recent primary literature identifies as determinants of outcome at a CD4 count below 200 cells/μL, and the resulting minimum data set.

Measurement	Why it was indicated in this patient	Documented?	What it would have changed
Obtained and used			
CD4 count	Defines advanced HIV disease and drives the entire package of care	Yes	Correctly identified profound immunosuppression; never repeated over seven months
CD8 count	Measured in the same assay run as the CD4 count	Yes, but not interpreted	Yields a CD4/CD8 ratio of 0.02 at no additional cost
Syphilis serology (VDRL, TPHA)	Genital lesions in an adult with 20 lifetime partners; molluscum contagiosum carries an odds ratio of 16 for syphilis	Yes	Both non-reactive; appropriately excluded
Co-trimoxazole prophylaxis	Standard component of the advanced HIV disease package	Yes	Given at 960 mg daily
Indicated and not obtained			

Measurement	Why it was indicated in this patient	Documented?	What it would have changed
1. HIV-1 RNA viral load	The only test that separates virological failure from immunological non-response after 24 months of therapy	**No**	Would have determined whether the regimen needed changing; 52% of Asian patients attend sites without routine testing
2. Resistance genotype	Indicated where viral load exceeds 1000 copies/mL; NNRTI mutations occur in 7% of treated patients in West Java on the same regimen	**No**	Would have guided a switch away from efavirenz
3. Serum cryptococcal antigen	Recommended at CD4 <100 cells/μL; yield in ART-experienced patients with non-suppression is 10.5%, close to the 13.8% in naive patients	**No**	Would have detected or excluded a common and treatable cause of death at this CD4 count
4. Tuberculosis symptom screen with urine LAM	Component of the WHO advanced HIV disease package of care	**No**	Would have addressed the leading cause of death in advanced HIV disease
5. Documented adherence assessment	Adherence was recorded only as the patient's own account; depressive symptoms and food insecurity are measurable and addressable barriers	**No**	Would have distinguished non-adherence from true treatment failure
Worth adding where available			
6. C-reactive protein	A value ≥10 mg/L in outpatients with CD4 ≤200 cells/μL was associated with 30-day hospitalization (relative risk 4.2) and death (relative risk 9.8)	**No**	Would have stratified 30-day risk at the index visit

Notes: *No World Health Organization clinical stage was assigned at any visit, so the clinical criterion that runs in parallel with the CD4 criterion was absent from the record as well. ART, antiretroviral therapy; LAM, lipoarabinomannan; NNRTI, non-nucleoside reverse transcriptase inhibitor; TPHA, Treponema pallidum haemagglutination assay; VDRL, Venereal Disease Research Laboratory; WHO, World Health Organization.*

First, an HIV-1 RNA viral load, taken at the dermatology visit itself rather than referred onward. It is the single measurement that separates virological failure from immunological non-response, and the entire subsequent management pathway diverges on the result. Second, a resistance genotype where the viral load exceeds 1000 copies/mL, because a patient failing on efavirenz in a region where non-nucleoside reverse transcriptase inhibitor mutations are documented in 7% of treated patients[32] requires a regimen change and not encouragement to adhere. Third, a serum cryptococcal antigen, on the evidence that the yield in antiretroviral-experienced patients with non-suppression is 10.5%, closely comparable with the 13.8% yield in the treatment-naive group in whom screening is routine.[45] Fourth, a tuberculosis symptom screen with urine lipoarabinomannan where available, as a component of the advanced HIV disease package.[42] Fifth, a documented adherence assessment, since adherence is measurable and its barriers are addressable.[39] A sixth measurement, the final row of Table 5, is C-reactive protein, worth adding wherever it is available, given its performance in stratifying 30-day risk in outpatients with advanced disease.[44]

None of these is a specialist investigation, and none appears in the obtained-and-used section of Table 5. All are available in the Indonesian public health system. The two blocks of Table 4 and the middle block of Table 5 make the same point from different directions. The point of the audit is not that this patient's clinicians failed where others would have succeeded, but the opposite: the omissions replicate exactly the pattern documented in large programmatic studies, in which 52% of Asian patients attend sites without routine viral load monitoring[33] and only 11.5% of eligible antiretroviral-experienced patients receive cryptococcal antigen screening.[45] The dermatologist is often the specialist who sees these patients first, because the skin declares the failure before anything else does. That position carries a corresponding responsibility.

3.11. Sexually transmitted infection screening and partner management

The genital origin of the first lesion, illustrated in Figure 1D and dated in Figure 5, the history of 20 lifetime partners including commercial sex workers, and condomless intercourse together place this case within sexually transmitted infection practice as well as dermatological practice. Syphilis screening was appropriately performed and was non-reactive on both treponemal and non-treponemal assays. The case-control data showing markedly raised odds of syphilis, chlamydia, condyloma acuminata and genital herpes in adults with molluscum contagiosum[17] argue for a broader screen than was documented here, and the clinical study of genital molluscum contagiosum in the reproductive age group[57] reinforces that genital molluscum contagiosum in an adult should be managed as a sexually transmitted infection with the partner notification that implies. Counselling on partner reduction and condom use was given and is recorded. Partner notification is not recorded, and in a patient whose last reported sexual contact was two years before presentation the tracing window had long closed; the omission is noted rather than criticized, but a documented decision, one way or the other, belongs in a venereological record.

3.12. Pruritic papular eruption as a second concordant sign

The limb eruption shown in Figure 1E and Figure 1F should not be treated as an incidental finding. Pruritic

papular eruption is one of the commonest HIV-associated dermatoses and is associated with lower CD4 counts; it features in the spectrum described in retrospective series of cutaneous manifestations,[60] in studies relating dermatological manifestations to CD4 count,[5] and in immunogenetic work examining human leukocyte antigen class II polymorphisms and cytokine levels in people living with HIV who have HIV-related dermatoses, including pruritic papular eruption, in a study of 115 patients against 80 controls.[61] The clinical value here is corroborative: two independent CD4-dependent dermatoses appeared within six months of one another, both after therapy had begun, an interval that Figure 5 makes visible at a glance. That combination is itself a strong indicator of profound immunosuppression, in the same way that late-onset opportunistic infection is: in a retrospective cohort of 10,583 treatment-naive patients followed for a median of 5.4 years, a late opportunistic infection occurred in 895 (8.4%) at a median of 2.1 years after starting therapy, tuberculosis accounting for 39% of them, and a treatment switch was among the independent risk factors (hazard ratio 1.31).[62] In a separate cross-sectional study of 223 patients receiving therapy, 57.9% had developed an opportunistic infection, and male sex and a low CD4 count were the correlates of onset.[63] Where no laboratory CD4 count is available, two concurrent CD4-dependent dermatoses carry the same message as those cohorts do.

3.13. Limitations

Several limitations constrain what can be concluded. This is a single case, and inference from one patient to practice is necessarily provisional. No HIV-1 RNA measurement exists at any time point, so the mechanism of immunological failure cannot be established and is discussed only as a differential. The cause of death is not documented, no autopsy was performed, and the death is therefore reported as a temporal fact and not attributed to any specific process. Adherence is recorded as the patient's own account and was not objectively verified. The dermoscopic images available for reproduction as Figure 2A and Figure 2B do not resolve the vascular structures recorded in the notes. The histopathological photomicrograph of the low-power field reproduced as Figure 2D was archived at a resolution below the journal's usual expectation and has been interpolated for reproduction, which is disclosed here. The source record described the body mass index of 25 kg/m² as normal weight, which conflicts with the World Health Organization Asia-Pacific classification; the discrepancy is flagged in Table 1 and reported rather than resolved. Table 3 records the evidence as the literature stands and does not constitute a formal risk-of-bias assessment, and Table 5 audits the record against current recommendations rather than against a validated instrument. Finally, the comparison presented in Table 4 draws on published case reports whose data elements were collected for other purposes and are not uniformly reported; it is offered as a structured juxtaposition rather than as a systematic review.

4. Conclusion

A 39-year-old man with HIV developed multiple giant molluscum contagiosum involving the eyelids, face, neck, hand and penis, together with pruritic papular eruption, and died seven months later. The lesions were diagnosed correctly, confirmed by the three independent techniques shown in Figure 2, and treated effectively: the facial disease had cleared by month 3, as Figure 4 shows. What was missed was not the dermatological diagnosis but its meaning.

Both eruptions arose after antiretroviral therapy had been started, and after 24 months of therapy the CD4 count was 31 cells/μL with a CD8 count of 1624 cells/μL and a CD4/CD8 ratio of 0.02. In a treatment-naive patient such findings call for antiretroviral therapy to be started. In a treated patient they call for the therapy to be interrogated, and that interrogation never took place. The comparison in Table 4 with a patient of identical CD4 count whose molluscum contagiosum and Kaposi sarcoma both resolved on antiretroviral therapy alone shows how much turned on that difference, and the final column of Table 3 explains why destructive treatment could not close the gap on its own.

Three conclusions follow. First, giant molluscum contagiosum arising on antiretroviral therapy should be read as a visible marker of treatment that is not working, not merely as a marker of advanced disease. Second, the CD4/CD8 ratio should be calculated whenever both counts are available, since it is free, it integrates CD4 depletion with CD8 expansion, and it carries independent prognostic weight. Third, the dermatological consultation at which this eruption is recognized should itself generate the five measurements set out in Table 5: a viral load, a resistance genotype where indicated, a serum cryptococcal antigen, a tuberculosis screen and a documented adherence assessment. In a patient with advanced HIV disease whose genital lesions also mark a sexually transmitted infection, full screening and partner management complete the response. Excising the nodules addressed what could be seen; the five missing measurements addressed what killed him.

Declarations

Use of Generative Artificial Intelligence. The authors declare that no generative artificial intelligence tool was used in the conception, research, analysis, drafting, revision or preparation of this manuscript, or in the production of any figure or table within it. All text, clinical data, interpretation, conclusions and clinical judgements are the authors' own, and every reference was retrieved and verified manually against the primary source: each digital object identifier was checked for registration with Crossref, the bibliographic fields were compared field by field with the publisher record, the full text or full abstract of every cited article was read, and every numerical value quoted in this manuscript was matched to the sentence of the source that states it, together with its denominator. The authors accept full responsibility for the content of the manuscript.

Author Contributions. A.Y. examined the patient, collected and curated the clinical data, prepared the figures and drafted the manuscript. E.Y.E. supervised the dermatological

management, contributed to the interpretation of the immunological data and critically revised the manuscript. A.M. contributed to the diagnostic work-up, the histopathological correlation and the literature appraisal. P.M. conceived the framing of the case, supervised the care-gap audit and critically revised the manuscript for important intellectual content. All authors read and approved the final version and agree to be accountable for all aspects of the work.

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Conflict of Interest. The authors declare that they have no competing interests, financial or non-financial, in relation to this work.

Ethical Approval. This case report was prepared in accordance with the Declaration of Helsinki. Institutional ethical clearance for the publication of anonymized clinical material was obtained in accordance with the policy of Dr. Moewardi General Hospital, Surakarta. No experimental intervention was undertaken; all treatment described was delivered as part of routine clinical care.

Patient Consent. Written informed consent for publication of the clinical history and of the clinical, dermoscopic and histopathological images was obtained. The ocular region has been masked in every photograph in which the face is visible, and no name, date of birth, medical record number, admission date or institutional identifier appears in any image or in the text.

Data Availability. All data supporting the findings of this report are contained within the article. The source clinical record cannot be shared because it contains identifying patient information.

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