Community Dermatology

The contribution of dermatology in the recognition and care of HIV-infected patients

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Introduction

Despite considerable public health efforts in reducing disease transmission and advances in developing more effective and tolerable anti-retroviral therapy (ART), the global burden of HIV continues to increase. Disorders of the skin are readily visible and provide a window to underlying disease including infection. Skin diseases are a commonly reported complaint in HIV-infected individuals with more than 90% developing at least a single disease of the skin or mucous membranes during the course of their HIV infection [Sud, 2009]. The skin and mucosae can be sensitive markers of underlying immunosuppressive states, and mucocutaneous diseases are often the first manifestation of HIV infection and advancing immunodeficiency. Since the very beginning of the HIV pandemic, dermatologists have accrued considerable knowledge of the atypical manifestations of common skin diseases that are indicators of HIV infection. As a result, even in resource-poor regions of the world without ready access to diagnostics, dermatologists have the skills to identify HIV infection. Furthermore, studies correlating the spectrum of HIV-related skin diseases with T helper CD4 cell counts and the degree of immunosuppression [Munoz-Perez, 1998; Sud, 2009] enable dermatologists to ascertain the probable level and advancement of immunosuppression based on the pattern of skin diseases they see in HIV-infected patients. In recent years with the growing recognition of immune restoration/ reconstitution-associated diseases, which include a number of skin diseases, dermatologists are also in a position to differentiate skin diseases associated with immune restoration as opposed to immunodeficiency as a consequence of the failure of ART.

This paper discusses the significant contribution of dermatology and dermatologists in the early recognition of the HIV virus in the 1980s, and also the important role that dermatologists today have in identifying underlying HIV infection early in the course of its disease as well as the myriad of opportunistic infections that HIV-infected patients are predisposed to.

The discovery of HIV

A dermatological disease played a pivotal role in the initial detection and recognition of HIV in the early 1980s in the USA. It was the atypical presentation of Kaposi's sarcoma (KS), a readily identifiable cutaneous tumour that alerted clinicians in New York to a unique underlying immunosuppressive state. Hitherto, KS was more commonly recognized as a benign disease of elderly men (classical KS) or a more aggressive disease associated with long-term immunosuppressant therapies (iatrogenic KS). In 1981 the Lancet reported eight cases of an

aggressive form of KS in young, homosexual men who were not on any form of immunosuppressant therapy [Hymes, 1981]. At around the same time aggressive cases of KS were also described in association with pneumocystis carinii pneumonia, the incidence of which was reported to have significantly increased in homosexual men in both the East and West coasts of the USA [MMWR Weekly, 1981]. As a result of these reports the Centers for Disease Control (CDC) in Atlanta formed a Task Force on Kaposi's Sarcoma and Opportunistic Infections (KSOI) [University of California, 1995]. Until the HIV virus was detected and the acronym 'AIDs' coined, this new and as yet unidentified disease was often known as 'KSOI' in recognition of the constellation of diseases seen in affected patients. AIDS was finally defined by the CDC on the basis that it was an acquired rather than an inherited condition, because it resulted in a deficiency within the immune system, and because it was a syndrome consisting of a number of manifestations as opposed to a single disease entity. In the early 1980s, there were reports also from Western Europe suggesting two separate AIDs epidemics, one predominantly affecting the white homosexual community and a second epidemic affecting immigrants from central African countries [Clumeck, 1984]. At the same time clinicians in Zambia and Zimbabwe reported an aggressive and fatal form of KS [Bayley, 1984; Coker, 1986], which was clinically distinct from the well-recognized African endemic KS. African endemic KS occurs predominantly in Central Africa and the Rift Valley region of East Africa but it runs a benign course much like classical KS. The detection of an immunosuppression-related KS alerted clinicians to the emergence of AIDs in this region of the world as well. The virus responsible for AIDs was only identified and reported later in 1984 after these developments. In conclusion, our recognition and knowledge of KS played a pivotal role in the definition and understanding of the aetiology of AIDs.

HIV immunodeficiency-associated skin disease

HIV infection is characterized by a period of silence and those infected with the virus outwardly may appear and feel healthy with no overt signs or symptoms of immunosuppression for many years. This poses a considerable public health risk as the HIV-infected patient who is unaware of his/ her HIV status may infect others with the virus. The dermatological manifestations of HIV immunosuppression have been extensively described in the medical literature since the earliest recognition of HIV and AIDs. This has given dermatologists the considerable advantage of being able to detect underlying immunodeficiency. The dermatologist is therefore in the unique position of considering HIV testing in patients early in the course of their infection when they present with any of the skin diseases described in association with HIV infection. The early recognition of HIV infection is critical because it is associated with an improved prognosis.

The spectrum of dermatological conditions seen in HIV-infected individuals is vast. The dominant HIV immunodeficiency-associated skin diseases are infectious and inflammatory and they can cause significant morbidity. Although skin cancers are less common their prognosis is often worse. Clinical presentations of skin disease in HIV-infected patients are often atypical and may vary depending on the level of immunosuppression. Managing skin disease in the context of advanced immunosuppression is challenging and they often respond poorly to conventional therapies [Ameen, 2010]. Certain skin diseases or atypical clinical presentations of more common skin diseases can alert the clinician to underlying HIV infection: recurrent or multi-dermatomal herpes zoster, recalcitrant viral warts, KS and severe seborrhoeic dermatitis are good examples. The commonest skin disease affecting HIV-infected individuals is seborrhoeic dermatitis, which is seen at every

stage of HIV infection, increasing in frequency at lower CD4 counts. Its severity correlates with a poor overall prognosis [Mathes, 1985]. It deteriorates with advancing immunosuppression becoming widespread and therapy-resistant. It often only responds to conventional therapies after the commencement of ART and immune restoration [Dunic, 2004]. Seborrhoeic dermatitis is the third commonest cause of erythroderma in HIV infection after drug reactions and psoriasis [Morar, 1999]. Erythroderma is potentially fatal and seborrhoeic dermatitis as a cause of erythroderma is almost unheard of in immunocompetent individuals. Seborrhoeic dermatitis is one of a range of pruritic disorders that afflict HIV-infected individuals. Others include atopic eczema, numerous causes of folliculitis, and photodermatitis. In addition, severely immunocompromised patients commonly complain of HIV-associated pruritus: its diagnosis requires the exclusion of primary pruritic skin diseases, drug reactions, systemic disease and metabolic abnormalities. Its clinical manifestations include excoriations, linear erosions and secondary eczematous changes. Xerosis, or dry skin, is common with late-stage HIV infection: it is reported to have an incidence of 19% in CDC stage II disease and 51% in stage IV disease [Muñoz-Pérez, 1998]. Xerosis itself can be a cause of pruritus and may trigger atopic eczema and potentially aggravate any inflammatory skin disease.

Adverse drug reactions are more common with HIV infection compared to uninfected patients with a reported prevalence of 14-18%, the risk increasing with advancing immunosuppression presumably because of immune dysregulation [Coopman, 1993; Muñoz-Pérez, 1998]. In the HIV-infected population all types of drug reactions are more severe and in addition, the prevalence of life-threatening drug reactions such as Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are significantly higher [Muñoz-Pérez, 1998]. The most commonly incriminated drugs include sulphonamides, aminopenicillins and antituberculous drugs, which are often the drugs most frequently prescribed to HIV-infected patients. Dermatologists need to highlight the risks to other clinicians of inappropriate drug prescribing in HIV-infected patients and the potentially devastating consequences. Nurses with experience of caring for skin conditions can play an essential role in the management of diseases such as TEN. Optimal nursing care with particular attention to the prevention of sepsis and promoting skin re-epithelialization can considerably decrease the risk of mortality and significant morbidity associated with TEN.

Some diseases may be indicative of the patient's immune status as they characteristically manifest at certain CD4 counts: eosinophilic folliculitis, molluscum contagiosum and chronic herpes simplex infection occur in advanced immunosuppression [Muñoz-Pére, 1998]. Multiple disorders of the skin and mucosae are common, particularly with advancing immunosuppression, and in these clinical scenarios the dermatologist can more confidently predict underlying immunosuppression and its severity [Muñoz-Pére, 1998; Sud, 2009].

In the assessment of patients dermatologists routinely examine the mucosae. This is particularly advantageous in the HIV-infected patient as mucosal disease is common but often asymptomatic. Consequently mucosal disease is often overlooked and yet a number of oral diseases provide ready indicators of underlying immunosuppression. These include oral candidiasis, which is the commonest mucocutaneous infection of the HIV-infected patient [Sud, 2009]. Its incidence is significantly higher with increasing CDC stage: 12% and 50% among those with stage II and IV disease respectively [Muñoz-Pére, 1998], and studies demonstrate that it is significantly associated with disease progression [Smith, 1994]. Oral hairy leukoplakia, which produces characteristic

lesions on the tongue and oral mucosa, occurs as a result of Epstein-Barr virus infection and proliferation within the epithelial cells. It is a sensitive marker of underlying immunosuppressive states including HIV infection. It can occur at any stage of HIV infection but is more common with advanced immunosuppression, particularly with CD4 counts of less than 200/µl [Husak, 1996]. KS, the first recognized cutaneous marker of HIV infection and an AIDS-defining malignancy, commonly affects the oral mucosa. KS may also first manifest in the oral cavity and furthermore, mucosal KS may provide an indicator of systemic involvement. Therefore, the dermatologist's routine examination of the mucosae may not only suggest HIV testing but may support the diagnosis of AIDs.

Skin disease after initiation of ART

The introduction of ART has significantly increased the life expectancy of HIV-infected individuals and generally improved their quality of life. Its implementation and generalized use has lead to a change in the spectrum of HIV-associated dermatological disease. There has been a decrease in the prevalence of all skin diseases, particularly opportunistic skin infections. In addition, skin diseases associated with HIV infection are less severe and easier to treat with ART and consequent immune restoration [Maurer, 2004]. However, with increasing HIV infection rates in some groups and populations and the movement of migrant populations who are not been able to access regular healthcare, it is not uncommon for newly diagnosed HIV-infected individuals to present with advanced immunosuppression and associated dermatological disorders. Therefore, despite the general decline in HIV skin disease in the era of ART, knowledge of HIV-related mucocutaneous diseases remains important. Furthermore, ART itself is associated with additional dermatological problems: drug-related adverse effects, both acute drug reactions as well as insidious long term changes to the skin and associated structures, and immune restoration syndrome (IRS)-related skin diseases. In addition, as a result of ART significantly increasing the life expectancy of HIV-infected individuals, dermatologists have seen a significant increase in skin cancers in this group of patients. Although ART appears to be protective of AIDs-defining malignancy such as KS, there has been a dramatic rise in HPV-related anogenital cancer [Chaturvedi, 2009], and HIV immunosuppression predisposes HIV-infected individuals without significant risk factors to a higher incidence of non-melanoma skin cancers with a more aggressive clinical course [Crum-Cianflone, 2009].

IRS occurs as a response to ART with suppression of viral load and an increase in CD4 count. It arises from restored immunity to specific infectious and non-infectious antigens resulting in a paradoxical clinical worsening of a known condition ('paradoxical IRS') or the appearance of a new condition ('unmasking IRS') [French, 2000]. Estimates suggest that IRS affects 10-25% of unselected adults who are commenced on ART [Murdoch, 2008] and the incidence is even higher in those patients with prior opportunistic infections. The skin is the most commonly affected organ accounting for 51-78% of IRS-associated conditions [Lehloenya, 2006; Huiras 2008]. Both infective and non-infective skin diseases have been associated with IRS and they may present in an atypical, inflammatory, refractory or paradoxical manner. Given that many HIV-infected patients carry a high antigen burden prior to initiation of ART, IRS-related skin disease is most commonly an inflammatory reaction to an opportunistic infection: mucocutaneous warts, herpes simplex and varicella zoster virus infections are the most frequently reported IRS-associated dermatological events. Unlike the more serious diseases associated with IRS such as cryptococcosis and tuberculosis, IRS-associated skin diseases are rarely fatal, usually respond to conventional

therapies, and do not necessitate ART withdrawal. Susceptibility to IRS-associated dermatologic events at the time of ART initiation has been reported to be associated with advanced disease by WHO staging and low CD4 counts, which were often less than 50-200/µl [French, 2000; Murdoch, 2008; Osei-Sekyere, 2010]. This is consistent with risk factors for other IRS-associated conditions [French, 2000; Murdoch, 2008]. There is now growing recognition of the wide range of IRS-related skin diseases and it is critical that the clinician caring for the HIV-infected patient does not mistake them for an immunodeficiency-related disease and suspect ART failure. Therefore, dermatologists who take an active interest in HIV disease and its dermatological manifestations can play a critical role in ensuring correct disease classification and optimal management of the HIV-infected patient. The high prevalence of skin diseases with HIV immunosuppression has meant that HIV-infected patients often associate skin rashes with the advancement of their HIV infection and a poor prognosis. Consequently, the development of severe IRS-associated skin diseases may lead some patients to discontinue their ART. If patients on ART have ready access to dermatological services, the dermatologist is in a position to educate and counsel them before ART initiation and reassure them in the event that they develop IRS-associated skin diseases that these will improve with continued ART and conventional treatment for their skin disease.

The direct adverse effects of anti-retrovirals (ARVs) can be short- or long term and include drug-related rashes and appearance-related side-effects such as lipodystrophy syndrome. HIV lipodystrophy syndrome occurs as a result of ART-induced metabolic abnormalities leading to changes in fat distribution. It can be cosmetically very disfiguring and have a significant psychological impact on patients. This has potentially serious consequences in terms of decreased adherence to therapy, which can result in regimen failure and the development of drug resistance. Nucleoside reverse transcriptase inhibitors (NRTIs), particularly zidovudine and stavudine, and protease inhibitors are associated with the risk of developing lipodystrophy. The dermatologist is able to identify early lipodystrophy and recommend changes to ART regimens as lipoatrophy in particular may improve with ART regimen change. Dermatologists have also been involved in the surgical management of lipoatrophy employing autologous fat transplantation or facial fillers. Mucocutaneous and nail pigmentation are well-described adverse effects of ARVs and given that they also affect the appearance of the HIV-infected patient, they too can impact on ART regimen adherence. However, their effects are usually dose-dependent and reversible with dose reduction or drug withdrawal and therefore again the dermatologist may intervene in severe cases and advise a change in drug regimen if possible. Retinoid-like mucocutaneous adverse effects of protease inhibitors are common, particularly with indinavir. They are also reversible with drug discontinuation, which may have to be advised in severe and intolerable cases [García-Silva, 2002].

Acute drug reactions significantly increase after the introduction of ART, one study reporting an increase from 8% to 20% [Calista, 2002]. ARV-related drug rashes commonly occur soon after therapy initiation but are usually reversible or treatable. They are commonest with non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine and efavirenz. The dermatologist is able to identify and classify drug-related rashes and assess their level of severity thereby ensuring drug discontinuation in the event of severe drug reactions such as SJS and TEN or preventing unnecessary discontinuation of ARVs in milder cases. Both drug-related adverse effects and IRS-associated dermatological events occur within a similar time frame and may cause diagnostic difficulty for the non-dermatologist. This may result in IRS-associated skin diseases sometimes being mistaken for drug reactions leading to unnecessary discontinuation of ARVs.

Conclusion

The skin is the most common organ affected by HIV. Although HIV-related skin diseases are not a common cause of mortality they can cause considerable morbidity. They can be an early marker of underlying HIV infection as well as an indicator of advancing immunosuppression. In resource-poor settings where regular immunological monitoring is not always feasible, mucocutaneous disorders in HIV-infected individuals are key clinical indicators for predicting the underlying immune status, disease progression, and possible complications or failure of ART [Nnoruka, 2007]. ART has had a considerable positive impact on HIV immunodeficiency-associated skin diseases but has brought with it a different spectrum of skin disorders to challenge the dermatologist. Even in the present era of ART, HIV-associated skin diseases constitute a significant burden on health systems and adversely affect quality of life. Therefore, dermatology and dermatologists can still make a significant contribution to HIV medicine and the care of HIV-infected patients.

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