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Views and Practice

HIV and dermatosis

CK Kwan 關志強

It is common for the HIV-infected patients to present with skin problems. It has been suggested that around 86-96% of HIV-infected patients have mucocutaneous manifestations and there are approximately 2.4 skin problems for each patient.[1] HIV not only targets CD4 T lymphocytes, but also attacks the skin Langerhans cells and dermal dentritic cells. With the impaired function in these antigen presenting cells, the immune defense system of the skin is compromised. This is believed to be responsible for the frequent occurrence of infectious and non-infectious skin diseases in HIV-infected patients.

Table 1 shows the relationship between the CD4 count and HIV skin manifestations. In general, the lower CD4 count, the higher chance of opportunistic infection. Nonetheless, psoriasis manifests with paradoxical behaviour with HIV infection. Studies have shown that pre-existing psoriasis may undergo severe exacerbation in HIV-infected patients and become more severe with progression to AIDS,[2] and biologics may be considered after failing first-line treatments.[2]

Social Hygiene Service, Department of Health, Hong Kong

CK Kwan, MBBS(HK), FHKAM(Medicine)

Correspondence to: Dr. CK Kwan

Cheung Sha Wan Dermatological Clinic, 3/F West Kowloon Health Centre, 303 Cheung Sha Wan Road, Kowloon

Immune Reconstitution Inflammatory Syndrome (IRIS) basic mechanism

The Immune Reconstitution Inflammatory Syndrome (IRIS) refers to a collection of inflammatory disorders following the initiation of highly active antiretroviral therapy (HAART) in HIV-infected patients. The estimated prevalence varies from 10 to 30%.[3] In general, the mortality of IRIS is 4.5% but the proportion could be much higher if it is related to cryptococcal meningitis.[3] IRIS typically presents within the first few months of commencing HAART but may occur weeks to years after HAART initiation.

Immunopathogenesis of IRIS

The immunopathogenesis of IRIS is not clearly understood. Generally, it is a dysregulation of the immune response to a variety of antigenic stimuli after initiation of HAART. The immune response recovers after HAART initiation, but there is an imbalance of the immune system in terms of number of immune cell, immune cell function, defects in regulatory function as well as changes in Th cell profile. All these are essential factors in the pathogenesis of IRIS.

Definition of IRIS

There are no definitive markers for the diagnosis of IRIS and no single accepted definition. Clinically,

it requires the presence of worsening of a recognised (paradoxical IRIS) or emergence of an unrecognised pre-existing (unmasking IRIS) infection in the setting of improving immunological function. Other features includes low pretreatment CD4 count, clinically manifestations consistent with an inflammatory condition, a temporal association between HAART initiation and onset of the inflammatory condition, a positive virological and immunological evidence response to HAART and last but not the least, no evidence of adverse drug reaction, bacterial superinfection, or drug-resistant infection.

Why skin manifestations of IRIS are significant

Skin manifestations of IRIS are common and the inflammatory response of skin condition may also affect the quality of life of the patient. The skin is the largest organ of the human body, and serves indirectly as a very good visible marker for an appropriate response to HAART in resource-limited centres such as in poverty-stricken countries in Africa. Finally, IRIS itself can be fatal especially in cases of cryptococcal meningitis as previously mentioned. After HAART, the immune system becomes reconstituted. The restored inflammatory response can cause significant cerebral oedema in the HIV patient with cryptococcal meningitis which is detrimental and may even be fatal. Therefore, early recognition of the skin manifestation of IRIS is essential.

Cutaneous manifestations of IRIS

Different kinds of dermatoses differ in response to IRIS. We are going to describe the response of some common dermatoses:

I. Follicular inflammatory eruptions

Acneiform eruption or rosacea-like eruption is a

Table 1. Rough relationship with CD4 count and skin manifestation in HIV

Rough CD4 count cell/uL	Skin problems
Early infection >500	Acute viral syndrome
	Kaposi's sarcoma (KS)
	Wart
	Vaginal Thrush
Mild immunosuppression 200-500	Oral Thrush
	Recurrent Herpes simplex and zoster
	Recalcitrant seborrhoeic dermatitis
	Oral Hairy Leukoplakia
	Recalcitrant Psoriasis
	Hyperkeratotic Warts
Significant immunosuppression 100-200	Disseminated herpes infection
	Eosinophilic Folliculitis
	Wide spread molluscum
	Extensive KS
Advanced immunosuppression <100	Cutaneous Penicilliosis
	Non-healing and large herpes
	Cutaneous Cryptococcus
	Disseminated cytomegalovirus (CMV) infection

kind of IRIS cutaneous manifestation. A case series described an acneiform eruption or rosacea-like eruption occurring within four months after immune reconstitution.[4] Basically, the overall incidence of eosinophilic folliculitis has declined after the era of HAART but an upward surge has been noted in the first six months after the initiation of HAART particularly in patients with low nadir CD4 counts. This is due to immune recovery folliculitis – IRIS.

II. Neoplastic lesions

Kaposi's sarcoma (KS) is well-recognised in HIV infection and AIDS. The overall incidence of KS decreases with the commencement of HAART. Paradoxically, some reports have noted that an explosive eruption of new cutaneous KS lesions, with increased nodularity and vascularity of existing lesions or increasing KS-related oedema within the first weeks of HAART,[5] reflecting that IRIS is in progress.

III. Cutaneous infection

Cutaneous infections are very common in HIV-infected patients because of their impaired immunity. Therefore, cutaneous infections would also be an important cutaneous manifestation of IRIS. After initiation of HAART, the pattern of cutaneous infection is altered such as the unmasking of occult skin disease or paradoxical worsening of existing skin conditions.

Viral infections are commonly implicated in IRIS. For example, Varicella Zoster virus (VZV) infection is not rare in the general population and is also common in HIV-infected patients. One study suggested that although the overall incidence in individuals on HAART was estimated at 6.9 cases per 100 patient-years, the rate dramatically increased to 26.9 per 100 patient-years between four and 16 weeks after HAART initiation, reflecting the phenomenon of IRIS.[6] It has also been suggested that a high CD8:CD4 ratio or rapid increase in CD8 count are risk factors for the development of VZV as an IRIS manifestation after HAART initiation.[6]

Herpes Simplex virus (HSV) also has similar pattern with VZV. Studies have suggested that there is a significantly increased incidence of HSV in patients on HAART. There were up to 26.6 cases per 100 patient-years reported for less than two months after HAART which then normalised to 5.2 per 100 patient-years at six months after HAART.[7]

Molluscum Contagiosum (Pox virus) and Human Papilloma virus (HPV) manifestations are also exaggerated in IRIS. Onset of numerous cutaneous warts developing six weeks after HAART has been reported.[8] In another report, a 2 cm perianal wart in an HIV-infected patient that had been stable for 9 years, transformed into a giant Buschke-Lowenstein tumor after HAART initiation.[9]

IV. Autoimmune and other conditions

Autoimmune diseases such as lupus erythematosus, Graves' thyroiditis and alopecia areata and vitiligo are suggested to be associated with IRIS. A case report showed that a HIV-infected man developed alopecia universalis with total hair loss after initiation of HAART.[10] He also had mild proptosis with lid lag and resting tremor. Thyroid function tests showed hyperthyroidism with elevated both free T3 and free T4 level. Thyroid scan showed diffuse activity with markedly elevated uptake. Clinical diagnosis of Graves' disease was then established due to IRIS.[10]

Management and treatment

The above mentioned entities are only the more commonly seen IRIS-related cutaneous manifestations and the list is far from complete. The clinician should initiate symptomatic treatment and supportive care for patients with IRIS, while HAART should be continued and the standard treatment of the offending opportunistic infection should also be continued. If, in severe cases, the internal organs or functional status of the patients is deteriorating, (such as decline pulmonary function from TB, visual loss from CMV retinitis, neurological complication from cryptococcal

meningitis), systemic corticosteroids to suppress the inflammatory response may be needed. However, the use of corticosteroids needs to be balanced against the risk of immunosuppression leading to worsening of pre-existing infection and acquisition of new infections. Most of patients should respond to systemic steroid within days to weeks and expert care may be needed in this dilemma between severe IRIS and severe infection in HIV-infected patients.

Conclusion

IRIS is a dilemma condition after the initiation of HAART in HIV-infected patients. It may cause mortality especially in pre-existing cryptococcal meningitis. Cutaneous manifestations of IRIS may vary, depending on the type of dermatosis. Management includes symptomatic treatment and continuation of HAART. Expertise in HIV medicine and infectious diseases may be needed in difficult cases.

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