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Cutaneous Eruptions of Lymphocyte Recovery

Speaker: Thomas D. Horn

Erythematous macular and papular eruption after cyto-reductive chemotherapy for various neoplasms is a fairly common occurrence. The differential diagnosis includes adverse drug eruption, viral exanthem and infection. The speaker focused on certain conditions that are occurring at the time of peripheral leukocyte recovery and are termed cutaneous eruptions of leukocyte recovery. Three conditions can be identified: eruption of lymphocyte recovery, allogenic graft-versus-host disease and autologous graft-versus-host disease. Among the three, eruption of lymphocyte recovery is most interesting in that the mere recovery of lymphocyte can lead to an eruption.

Eruption of lymphocyte recovery

This occurs in patient undergoing marrow ablative therapy after a variable period of leucopenia. Erythematous macules appear with variable distribution and extent. There is acute temperature elevation and the peripheral lymphocyte 'blip' corresponding to the onset of eruption.

The speaker mentioned that this condition occurred in 10 out of 14 of his febrile patients after cyto-reductive therapy for acute leukaemia. Histology is rather non-specific: the upper dermis is infiltrated with lymphocytes; there is minimal exocytosis and spongiosis; and basal vacuolization with scattered necrotic keratinocytes. Although it is unknown why returning lymphocytes would be particularly adept at causing a rash, the concept unifies several exanthems. The speaker commented that the rash in measles could also be considered as a form of eruption of lymphocyte recovery.

Acute graft-versus-host reaction

Cutaneous eruptions occur in about 50% of patients and at time of peripheral lymphocyte recovery. The eruptions are similarly non-specific, with erythematous macules and papules, and commonly start acrally with follicular accentuation. A staging scheme has been advocated: Stage 1: <25% involvement, Stage 2: 25-50%, Stage 3: erythrodermic and Stage 4: vesicular and bullous.

Histopathology is more specific than eruption of lymphocyte recovery. The interface changes are more evolved than typical eruption of lymphocyte recovery. There may be confluent sub-epidermal cleft to separation of epidermis.

Autologous graft-versus-host reaction

The eruption appears in roughly 10% of patients at the time of lymphocyte recovery. The clinical and histological features are similar to eruption of lymphocyte recovery with variable erythematous maculopapular lesions. It is usually a self limited disease without visceral involvement and no treatment of the rash is necessary.

Diagnosis

It is important to know the type of treatment, the type of transplant, WBC count, and timing of the rash in relation to the cyto-reductive therapy and transplant. Oncologists often want to have the biopsy done promptly for a faint erythematous rash, when the histology is often not fully evolved. In this situation, perifollicular lesional biopsy may give more useful imformation especially in acute graft-versus-host reaction in which the eurption has a follicular accentuation. It is important to follow the progression of the rash. What looks like a drug eruption earlier on may turn out to be graft-versus-host disease several days later.

The Skin & HIV Infection

Speaker: Dr. T. G. Berger

The skin manifestation of HIV infection is ever-changing as the number of HIV patients, as well as their life spans, are increased significantly by various anti-viral and prophylactic therapy introduced in recent years. Dr. Berger presented a number of rare cutaneous manifestations or atypical presentations of HIV dermatoses in patients whom he managed.

Helicobactor cellulitis: a new entity

This newly defined infection occurring in HIV patients usually presents with painful erythematous nodules and round or annular tender plaques in the lower limbs. The eruption has a subacute to chronic onset in weeks to months, and is gradually progressive. The lesions are usually multicentric in distribution, especially involving the lower limbs. The morphology of individual lesion may closely resemble and often be misdiagnosed as erythema nodosum. Systemic upset with fever is common and Helicobactor cinaedi bacteremia may occur in 40-60% of patients, though episodes of hypotensive septic shock are rare. Monoarticular arthritis occur in 20% of patients. Gastrointestinal symptoms such as diarrhea and abdominal pain were reported in 22-35% of patients. The sources of Helicobactor is believed to be originated from the gastrointestinal tract. The correct diagnosis on this relatively new condition depends on a high index of suspicion in person at risk, such as those who are homosexual and HIV positive, or immunosuppressed. Microbiological diagnosis requires special handling of blood and stool specimen for culture of the organism in a hydrogen rich environment. Skin biopsy can confirm the diagnosis of cellulitis and exclude other differential diagnoses such as panniculitis. The top-of the list differential diagnoses of pretibial nodules in HIV patients should include various uncommon infective causes such as acanthamoeba, bartonellosis and brucellosis. It is also important to note that erythema nodosum, being basically an antibody-antigen immune response, is relatively uncommon in immuno-compromised host, especially in HIV patients. Treatment depends on the variable antibiotic sensitivities of Helicobactor and reliable cure can be obtained by giving six to eight weeks of oral clarithromycin 500mg BD or Ciprofloxicin 500mg BD. Longer course of systemic antibiotics may be required, otherwise relapses are not uncommon.

Acute HIV Seroconversion Syndrome: one virus, more than one exanthem

Symptomatic acute seroconversion occurs in about one per cent of HIV patients. The clinical features, which simulate flu or infectious mononucleosis-like illness, occur several weeks after exposure. About forty percent of patients are fairly ill during the acute phase. Sorethroat and adenopathy are common. In a small study by the speaker, almost 100% of patients had skin eruption during the acute seroconversion and about 75% of patients had abnormal physical examination. Unlike ordinary viral exanthem with maculopapular or morbilliform morphology, the HIV exanthem is more papulosquamous simulating pityriasis rosea. In addition, many HIV patients may also present with a monomorphic papular eruption on upper chest, limbs and face, somewhat simulating papular acrodermatitis of childhood but occurring in adult. Some patients may develop bullous eruption. Mucocutaneous findings include oral apthous-like ulcer, which may extend into esophagus, and genital ulceration are not uncommon. Differential diagnoses include pityriasis rosea, syphilis and other viral exanthem caused by EBV, CMV or parvovirus B19, etc. Biopsy on skin lesion is only suggestive of viral exanthem but it is neither diagnostic nor specific for HIV acute seroconversion. The definitive diagnosis depends on ELISA test for HIV antibody, T helper cell count (but beware of CD4 lymphopenia which also occurs in other viral illness), and more importantly HIV viral load (especially in those suspected patients whose ELISA test for HIV antibody are initially negative during the very early phase of the disease). Treatment for HIV acute seroconversion syndrome is by Highly Active Anti-Retroviral Therapy (HAART) that consists of triple antiviral agents to decrease the viral load. There have been reported cases of relapses of seroconversion syndrome as HAART was reduced or stopped in some patients. In this condition, Dr. Berger concluded by bringing up a new paradigm of viral exanthem, in which the previous belief is that one virus causes one type of exanthem (e.g. varicella causes multiple crops of papulovesicular eruption in different phases recognized clinically as chickenpox). But now a new concept of one virus causing more than one type of exanthem is increasing acknowledged as seen in HIV acute seroconversion which may present with different morphological appearances.

Modification of HIV related skin eruption by Highly Active Anti-Retroviral Therapy (HAART)

HAART and Eosinophilic Folliculitis

Eosinophilic folliculitis (EF) occurs quite frequently in HIV patients. It typically presents with very itchy follicular papular eruption with 90% of lesions distributed above the nipple line. The definite diagnosis can be made by the typical morphology and

distribution of the lesion and skin biopsy on affected follicles. It has been increasingly recognized that triple anti-retroviral therapy may actually cause an acute flare of EF. It is important to recognize that the flare of skin eruption is due to eosinophilic follicultis and is not caused by drug eruption. As a result, there is no need for stopping HAART. Instead, an effective modality for treating EF is added on the top of HAART. Among the different treatment modalities available, Dr. Berger considered phototherapy is the treatment of choice. It is because itraconazole may interact with protease inhibitor in these patients. Isotretinoin and protease inhibitor may simultaneously worsened the lipid profile and their concomitant use in these patients is also not desirable. Dr Berger also pointed out that drug eruption due to HAART is rare except with Nevirapine which infrequently caused Steven-Johnson's syndrome. Most "adverse skin reaction" with HAART are flare of EF. Finally, worsening of preceding eczema may also occur with the use of Indinavir.

HAART and drug eruption

HAART is associated with severe drug eruption with concomitant use of cotrimoxazole. Patient presents with severe generalized systemic illness, high fever, exanthem and conjuctivitis similar to Steven Johnson's syndrome. This severe drug eruption may occur suddenly despite a long preceding history of intake of cotrimoxazole with no adverse cutaneous reaction. Treatment is by giving systemic steroid and cotrimoxazole should be stopped.

HAART and other HIV skin diseases

HAART improves Kaposi's sarcoma, molluscum, psoriasis and vasculitis associated with HIV infection. But HAART may worsen pruritic eruption of HIV infection (e.g. eosinophilic folliculitis) and wart infection of different type, probably as a result of improved immune response which causes the flare of these diseases.

HIV-related fat redistribution: a new cosmetic stigma for HIV patient

Abnormal fat redistribution in HIV patients on HAART was first reported in 1997. These patients presented with loss of fat in cheeks (64% of patients occurring in cheeks and temporal region), extremities such as arms (64%), legs and buttocks (57%). There is an increase of fat in upper back (36%), and neck (29%) giving rise to a buffalo hump, and increase of fat in breast and intra-abdominal area. The sunken cheeks, in the form of a "pseudo-lipodystrophy look", on the face is becoming a more and more widely recognized new cosmetic stigma of HIV infection in this group of patient. The aetiology of this condition is not clear at the present moment. However, the condition is associated with the use of HAART triple cocktail therapy in HIV patients who are more likely to be given protease inhibitors. The endocrinological profiles in these patients were normal and there was no evidence of Cushing's disease. As the cosmetic appearance of the condition carries a considerable stigma, cosemtic surgical treatment with fat transfer and implantation in area of fat loss, especially in the face; as well as removal of fat by liposuction at buffalo hump were carried out.

Learning points:

The "pseudo-lipodystrophy" sunken cheeks and the buffalo hump are increasingly recognized as a new social and cosmetic stigma for patient who suffers from HIV-related fat redistribution.

Immune Restoration Syndrome: a new application of an old concept to HIV patients

This recently described phenomenon refers to the clinical presentations which occur as a result of the restoration of immune function after the administration of HAART in HIV patients. These include the appearance of tuberculide-like skin eruption after HAART in HIV patients whose AFB infection have already been treated previously. New appearance of sarcoidosis in HIV patients after HAART was also reported. The resolution of Kaposi's sarcoma, molluscum and plane wart were noted, but the flare of eosinophilic folliculitis and pruritic papular eruption; and the appearance of eczematous dermatitis after HAART in these patients were not uncommon. The mechanism of the phenomenon and its clinical diseases is believed to be due to the return of T helper cell function in a hyper-reactive state after HAART. In fact, this situation is not unique to HIV infection after treatment with cocktail therapy. Similar hyper-reactive immune status is seen in treatment of lepromatous leprosy with the development of reaction such as erythema nodosum leprosum, or during the recovery phase of bone marrow transplant with immune induced graft versus host disease.