Pemphigus vulgaris: A dermatological sequel of severe H1N1 infection

Sir,

Pemphigus vulgaris (PV) is an autoimmune disease characterized by blistering involving the skin and mucosa that develops due to interaction between predisposing genetic and environmental factors. Various infectious agents such as viruses of the Herpesviridae family have been implicated as stimulants of the immune system that eventually trigger PV. There have been no reports linking H1N1 infection to PV in the literature. Herein we report the case of a 50-year-old man who developed extensive PV within 15 days of recovering from life-threatening H1N1 infection.

A 50-year-old man presented with multiple fluid filled lesions all over the body and oral ulcers of 15 days duration. Onset was insidious with appearance of multiple lesions initially over legs, which ruptured easily leaving behind red, raw areas. Lesions progressively increased in size and number over the next 2-3 weeks to involve trunk and extremities and were associated with oozing of odorless, serous fluid and mild pain. Crusting was noted after two weeks. There was a history of erosions in the oral cavity which healed within one week. There was no history of fever, constitutional symptoms, dysphagia, hoarseness of voice, ocular or genital ulcers, photosensitivity, or significant weight loss. He had been admitted to a tertiary care hospital 15 days prior to onset of skin lesions with cough and breathlessness. Investigations that included nasopharyngeal swab for real-time polymerase chain reaction confirmed H1N1 infection. He was managed with mechanical ventilation: lung protective ventilation with optimal positive end-expiratory pressure along with dual antivirals (oseltamivir with zanamivir) for 7 days, parenteral antibiotics (teicoplanin and meropenem), and supportive care.

Dermatological examination revealed flaccid bullae with clear fluid, erosions, and crusted plaques distributed over trunk, both upper and lower extremities [Figure 1]. The Nikolsky's sign and bulla spread sign were positive. Examination of the oral mucosa, genitalia, palms, and soles was normal at the time of examination.

Tzanck smear showed acantholytic cells; histopathological examination revealed acantholysis and loss of intercellular bridges in epidermis. Intraepidermal bullae were present and dermis had focal infiltration by chronic inflammatory cells [Figure 2a]. Direct immunofluorescence (DIF) was positive for intercellular IgG and C3 [Figure 2b]. A diagnosis of PV was made and he was treated with dexamethasone cyclophosphamide pulse therapy with excellent response to treatment. He is presently in remission with no fresh lesions since two years.

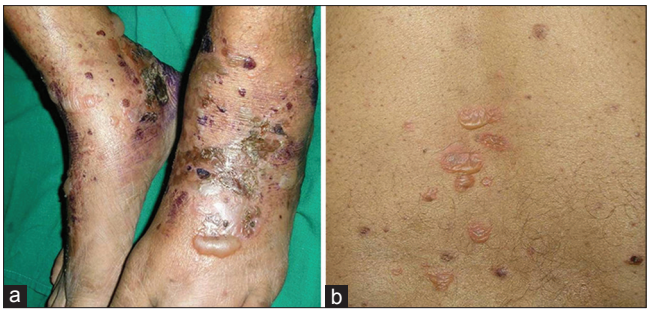

Figure 1: Multiple flaccid bullae and crusted plaques seen over both feet and back

The immunopathogenesis of pemphigus is not fully understood and has been explained on the basis of epitope spreading and molecular mimicry.[1] Infectious agents such as viruses can act in the following ways to trigger pemphigus: They stimulate the immune response in genetically susceptible individuals leading to an increase in production of interferon and interleukins. High levels of interferon-gamma induce the expression of HLA type 2 in the membranes of keratinocytes, making the structural site of PV antigen immunologically active (epitope spreading).[2] Microbes can also direct the release of cytokines and chemokines, whereas viruses can infect and selectively replicate in unique lymphocyte subsets and, by their presence, activation, or replication, cause immunosuppression or immunoenhancement. Another possible mechanism of association between viruses and PV is molecular mimicry, due to sharing of linear or conformational epitopes common to microbial antigens and host structures. This is an immunological phenomenon in which the primary immune response, usually to a pathogenic microorganism, cross-reacts with a self-antigen and causes autoimmune disease.[3]

Infectious agents, such as herpes simplex virus, Epstein–Barr virus, cytomegalovirus, and herpes virus 8 have been implicated in various studies as triggers for PV.[4] Thus far, pemphigus and linear IgA bullous dermatosis have been reported after influenza vaccination.[5,6] However, H1N1 infection or vaccination has not been linked to pemphigus in the literature. Neurological sequelae of H1N1 infection, such as multiple strokes, seizures, and encephalopathy, have been mentioned; however, there is a paucity of reports of dermatological sequelae post-H1N1 infection.[7] Only purpuric skin lesions and post-H1N1 vaccination-related skin lesions, such as erythema, unspecified skin rash, pityriasis rosea, urticaria, angioedema, and vasculitis find a mention in the literature.[8,9]

Drug-induced pemphigus was ruled out in our patient as the drugs administered to him are not known to trigger pemphigus. We therefore propose that the episode of H1N1 infection may have exposed intraepidermal epitopes to the immune system, resulting in the development of anti-intercellular antibodies and PV in our patient. To our knowledge, this is the first report of a case of PV developing soon after a life-threatening episode of

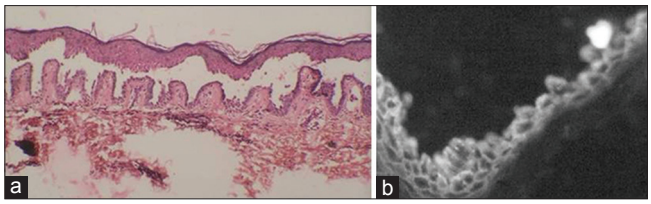

Figure 2: Histopathology showing intraepidermal bulla with acantholytic cells (H and E, ×40) and direct immunofluorescence of perilesional skin showing presence of C3 in the intracellular regions of the epidermis

H1N1 infection. The H1N1 virus may thus be acting as a trigger for autoimmunity in PV.

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