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Cutaneous involvement of disseminated adenovirus infection in an allogeneic stem cell transplant recipient

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Summary

Infection by human adenoviruses can lead to significant morbidity and mortality in immunocompromised hosts, such as allogeneic stem cell transplant (SCT) recipients, with limited effective treatment options. Specific cutaneous manifestations of disseminated adenovirus infection are not well described. We report a woman in her twenties who received an allogeneic T-cell-depleted peripheral blood SCT for the treatment of severe aplastic anaemia and, 5 months post-transplant, was hospitalized for severe systemic adenovirus infection with progressive involvement of the colon, liver and lungs. Despite therapy with intravenous cidofovir, oral brincidofovir and intravenous immunoglobulin, she had progression of adenoviraemia and dissemination of adenoviral disease. The patient developed a progressive rash characterized by keratotic papules that began on the palms and soles and spread to the entire body. Histopathological examination of skin biopsies of individual skin lesions from the palm and abdomen showed focal acantholytic dyskeratosis and keratinocytes with hyperchromatic nuclei. Several keratinocyte nuclei were immunoreactive for adenovirus. The patient was further treated with ribavirin and adenovirus-specific cytotoxic T lymphocytes but experienced multisystem progression of adenovirus infection culminating in death.

Adenoviruses are double-stranded DNA viruses that principally cause transient respiratory infections in immunocompetent hosts. Associated dermatological manifestations of adenovirus infections are nonspecific but include morbilliform/maculopapular eruption, unilateral laterothoracic exanthem, exanthem subitum-like rash, petechial rash, urticaria and Kawasaki disease.^{1–6} In immunocompromised hosts, clinical manifestations of adenovirus infection range from asymptomatic viraemia to pneumonia, hepatitis, encephalitis, cystitis, enterocolitis and disseminated infection, which is defined as multiorgan involvement in the presence of two or more adenovirus-positive peripheral blood polymerase chain reaction

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(PCR) assays and the absence of other identifiable causes.⁷ Disseminated infection carries a mortality rate up to 75%.⁷ Rates of adenovirus infection after stem cell transplant (SCT) range from 5% to 27%, depending on SCT types and method of adenovirus surveillance.^{8–10} Specific cutaneous manifestations of disseminated adenovirus infection are not well described. We report a case of fatal disseminated adenovirus infection in an allogeneic SCT recipient who developed a rash with unusual clinical and histopathological features.

Case report

A woman in her twenties with idiopathic severe aplastic anaemia successfully underwent a T-cell-depleted peripheral blood SCT from an 8/10 HLA-antigen matched unrelated donor. Her post-transplant course was complicated by Epstein–Barr virus (EBV) post-transplant lymphoproliferative disorder, involving primarily her tonsils, which was successfully treated with four weekly doses of intravenous (IV) rituximab 375 mg m⁻², third-party EBV-specific cytotoxic T cells and tonsillectomy. Five months post-transplant, the patient was admitted for diarrhoea and vomiting. On admission, her white blood cell count was 3.2×10^9 cells L⁻¹ (normal range $4.0\text{--}11.0 \times 10^9$ cells L⁻¹) and her total lymphocyte count was 0.1×10^9 cells L⁻¹ (normal range $0.5\text{--}5.3 \times 10^9$ cells L⁻¹). Adenovirus was detected by PCR assay of her stool (not detected in normal stool) and peripheral blood plasma (44 million copies mL⁻¹; normal range not detected), supporting a diagnosis of disseminated adenovirus infection. Her adenovirus type was type 2 by hexon typing from the blood specimen (Chimerix, Durham, NC, U.S.A.). The patient received IV cidofovir 5 mg kg⁻¹ on hospital days 3 and 9, oral brincidofovir (CMX001) 2 mg kg⁻¹ on days 17, 20, 24, 27 and 31, and IV immunoglobulin (IVIg) 400 mg kg⁻¹ on days 5, 6, 8, 10, 12, 14, 16, 24 and 31. Despite these interventions, her peripheral blood adenoviraemia persisted, ranging between 50 and 280 million copies mL⁻¹, and she had progression of adenoviral disease with additional involvement of the liver and lungs, as proven by biopsy and PCR assay of induced sputum, respectively.

On hospital day 31, dermatology was consulted for a 2-day history of rash on the bilateral hands characterized by itching and burning. She had no previous history of any dermatological conditions. Visual inspection revealed discrete 2–3-mm red papules on the palms, some with a vesicle-like appearance (Fig. 1). In the setting of recent IVIg administration, she was diagnosed clinically with IVIg-associated pompholyx.¹¹ The patient had not received any other medication associated with pompholyx or pompholyx-like reactions. She was treated with betamethasone dipropionate 0.05% ointment applied topically twice daily with no discernible improvement after 7 days. One week after consultation, new lesions appeared on the arms, trunk, legs and feet (Fig. 2). Close inspection and palpation of individual papules revealed that each lesion was composed of a firm, keratotic plug and that no fluid could be expressed. Owing to the rash progression, atypical morphology and absence of response to empirical topical corticosteroid treatment, skin biopsies were performed on the palm and trunk and IVIg was discontinued.

Histopathological examination revealed a unique constellation of findings characterized by small papular lesions of epidermal hyperplasia with a column of parakeratosis (Fig. 3). The keratinocytes underneath and adjacent to the parakeratotic column displayed focal

acantholytic dyskeratosis. Several had hyperchromatic nuclei. There was associated mild interface dermatitis. The hyperchromatic nuclei were immunoreactive for adenovirus [antiadenovirus antibody (M58 + M73), Abcam ab3648; Abcam, Cambridge, U.K.). No features of herpes virus infection were identified. The findings were interpreted as a cutaneous manifestation of adenovirus infection. A viral culture was performed on a swab specimen from a papule on the palm at the time of biopsy and was negative for herpes simplex virus and varicella zoster virus but positive for adenovirus, supporting the histopathological and immunohistochemical findings. There was no personal or family history of Darier–White disease.

The patient subsequently received a 13-day course of oral ribavirin 600 mg three times daily and a single IV infusion of third-party adenovirus-specific cytotoxic T lymphocytes. She experienced multisystem progression of adenovirus infection and disease with persistent peripheral blood adenoviraemia (range 2.9–99.0 million copies mL⁻¹), progression of rash with areas of erosions (Fig. 4), development of cholestatic hepatitis with positive adenovirus immunohistochemical stains on liver biopsy, pneumonitis, altered mental status and onset of hypoxaemic respiratory failure. The patient died on hospital day 81.

Discussion

In a 10-year retrospective study of 2879 allogeneic unmodified adult haematopoietic SCT recipients at the M.D. Anderson Cancer Center from 1999 to 2008, 73 (2%) patients were diagnosed with adenovirus infections, of which 18 (25%) were disseminated and 55 (75%) localized.¹⁰ Skin was not identified as an involved organ among any of the 73 confirmed cases of adenovirus infection, although one patient was reported as having had a skin rash as an initial clinical manifestation of infection. At the Memorial Sloan Kettering Cancer Center, a cohort of 624 adult and paediatric patients transplanted between January 2006 and March 2011 were assessed for rates of adenovirus viraemia and disease. These patients were recipients of both unmodified (36%) and T-cell-depleted (64%) grafts. The rate of adenovirus viraemia was 7% (n = 43), and 2% (n = 15) developed adenovirus disease. No patients developed skin lesions related to adenovirus⁹.

However, a previous study of 2889 adult SCT recipients at the M.D. Anderson Cancer Center from 1990 to 1998 identified two cases of disseminated adenovirus infection in which adenovirus was isolated from viral cultures of skin biopsies.¹² The histopathological findings of these skin biopsies were not illustrated and were reported as nonspecific; no immunohistochemical confirmation of adenovirus infection was performed and the clinical morphology of the skin lesions was not described. Nonspecific references to exanthem, skin rash, morbilliform eruption, petechial rash, meningococcemia-like rash and rubella-like rash have also been reported among immunocompromised and immunocompetent patients with disseminated adenovirus infection^{13,14}.

Hough et al. report a case of a 2-year-old patient with acute lymphoblastic leukaemia who developed fatal adenovirus hepatitis during first-line maintenance chemotherapy.¹⁵ His presentation was characterized by an acute febrile illness with diarrhoea, hepatosplenomegaly, vesicular rash, productive cough and pancytopenia. The skin biopsy

was reported to show epidermal necrosis, but the features were not illustrated. Adenovirus serotype 2 was isolated by enzyme-linked immunosorbent assay and culture from vesicular fluid. No clinical images from this patient were published.

We document a unique and novel cutaneous manifestation of adenovirus infection. Additional observations of cases of disseminated adenovirus infections with skin lesions are required to substantiate our findings and to determine relevant predisposing or modifying factors of adenovirus infection leading to skin involvement. We conclude that adenovirus infections in immunocompromised hosts can, rarely, involve the skin. Healthcare providers who evaluate patients with suspected disseminated adenovirus infection and rash should consider obtaining adenovirus PCR assay of peripheral blood and skin biopsy with adenovirus immunohistochemistry, when appropriate. Cutaneous lesions of disseminated adenovirus infection may include keratotic papules with a vesicle-like appearance. The distinct histological findings of parakeratotic columns associated with acantholytic dyskeratosis and keratinocytes with hyperchromatic nuclei should alert dermatopathologists to the likelihood of an adenovirus infection, which can readily be confirmed by immunohistochemistry.

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What's already known about this topic?

- Adenovirus infections mainly cause transient respiratory illnesses associated with nonspecific dermatological manifestations, such as morbilliform rash.
- Cutaneous involvement of disseminated adenovirus infection is not well described.

What does this study add?

- Skin lesions in disseminated adenovirus infections may appear as vesicle-like, red-to-violaceous, keratotic papules that initially favour acral sites.
- Histopathological features include parakeratotic columns associated with focal acantholytic dyskeratosis and keratinocytes with hyperchromatic nuclei that are immunoreactive for adenovirus.

Fig 1.
Clinical image of the palm. Individual vesicle-like papules composed of firm, keratotic plugs and surrounded by erythema.

Fig 2. Disseminated adenovirus infection. Clinical images highlighting keratotic papules on the (a) abdomen, (b) lower extremities and (c) palms.

Fig 3. Histological features. (a) Two separate small papular lesions with hyper- and parakeratosis (haematoxylin and eosin stain, original magnification $\times 20$); (b) adjacent keratinocytes are immunoreactive for adenovirus (antiadenovirus antibody, original magnification $\times 20$); (c) the epidermis surrounding the parakeratotic column shows focal acantholytic dyskeratosis. Several keratinocytes with hyperchromatic nuclei are present (haematoxylin and eosin stain, original magnification $\times 200$); (d) several keratinocytes are immunoreactive for adenovirus (antiadenovirus antibody, original magnification $\times 200$).

Fig 4. Later-stage cutaneous manifestations of disseminated adenovirus infection. Clinical images showing evolution of keratotic papules into erosions with areas of confluence on (a) palms and (b) face and ear.