Drug-induced systemic lupus erythematosus in a child living with HIV

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Abstract

Pediatric systemic lupus erythematosus (SLE) constitutes approximately 10% of SLE cases. The diagnosis and management of this condition remains to be a challenge in the pediatric population. The distinguishing clinical features are less pronounced male-to-female ratio, more organ damage, and higher disease activity compared to adult-onset disease. Drug-induced lupus erythematosus is rare in children. We report a case of drug-induced SLE in a child on antiretroviral therapy.

Key words: Antiretroviral therapy, HIV, lupus erythematosus, pediatric

Introduction

Drug-induced lupus erythematosus (DILE) is an autoimmune multisystem inflammatory disorder caused by autoantibodies formed after continuous drug exposure, associated with significant morbidity and mortality. DILE has rarely been reported in children. There is increased incidence of drug reactions in people living with HIV. Adequate knowledge of such reactions is essential for their appropriate management and improved quality of life in such patients.

Case Report

A 12-year-old previously asymptomatic boy was brought to the skin outpatient department with oral ulcers, skin rash, and fever of 5-day duration. He had been on antiretroviral therapy (ART) for HIV consisting of lamivudine, efavirenz, and abacavir, for the past 5 years. Cutaneous examination revealed diffuse involvement of the face, trunk, and upper limbs with nonscaly dusky macular lesions, multiple ulcers, and crusted erosions over the lips and hard palate. He was thin-built and underweight (18 kg). His developmental milestones were normal. Systemic examination revealed a temperature of 100°F with no other relevant systemic findings. Differential diagnoses of drug rash and viral exanthem were considered. He was managed with oral prednisolone 10 mg daily, tapered off over a period of 15 days, oral azithromycin 250 mg daily for 3 days, oral cetirizine 10 mg daily, care of oral ulcers, and supportive treatment for fever.

He showed a significant improvement of skin lesions, oral ulcers, and resolution of fever in 2 weeks. At this point, ART was reintroduced with tablet efavirenz.

Within 6 days of starting tablet efavirenz, he developed fever, erythematous nonscaly maculopapular rash covering the cheeks, nasal bridge, forehead sparing the nasolabial folds, trunk, B/L upper limbs, lower limbs, erythematous papules on the palms and feet, multiple ulcers, and crusted erosions over the lips and hard palate [Figure 1]. The rest of the cutaneous examination was normal.

There was no history suggestive of atopy, photosensitivity, joint pains, and similar complaints in the past. A family history revealed that both parents were living with HIV and were on ART for the same. Both succumbed to unknown complications six years back. Differential diagnoses of drug rash, drug-induced lupus, acute cutaneous lupus erythematosus, and COVID-19 infection were considered and he was admitted.

His laboratory investigations are mentioned in Table 1. His autoimmune profile revealed a positive antinuclear

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antibody (ANA) with a titer of 1:1000 (homogenous; grade +++), positive anti-double-stranded DNA antibody (anti-ds-DNA) titer above 800, low complement levels, and positive antihistone antibody (28 units). Skin biopsy findings include interface dermatitis, necrotic keratinocytes with perivascular and periappendageal inflammatory infiltrate suggesting the diagnosis of lupus erythematosus [Figure 2a,b]. Immunofluorescence study could not be done due to affordability. Considering his clinical, biochemical, and histopathological findings, a diagnosis of drug-induced lupus erythematosus (DILE) due to efavirenz was established.

Table 1: Investigations of the patient

Investigations	Values
Hematological investigations	Hemoglobin: 10 g/dL (12.5-16.5) Total leucocyte count: 3600 cells/mm^3 (4300-10,300), neutrophils: 57%, lymphocytes: 29%, lymphocytes: 29%, ESR: 45 mm/h (0-20 mm/h)
Liver functions	Aspartate aminotransferase (SGOT): 334 U/L (<51), alanine aminotransferase (SGPT): 108 U/L (<39), antihepatitis B antibodies: Negative
HIV related	CD4 count: 78 cells/mm^3 Viral load: 30 copies/mL
Immunological profile	ANA: Titer of 1:1000; homogeneous; Grade +++ Anti-ds DNA antibody: >800, complement C3 level: 36.7 mg% (80-180), complement C4 level: 12.2 mg% (10-40), antihistone antibody: Positive ++ (28 units)
Chest X-ray	Normal
USG abdomen and pelvis	Mild hepatosplenomegaly
Skin biopsy (from the right cheek)	Skin biopsy (from lesion on the right cheek): Basal layer vacuolization and interface dermatitis, superficial perivascular and perifollicular infiltrate composed of neutrophils and lymphocytes in the dermis [Figure 2a,b)
RT-PCR for COVID-19	Negative

ESR=Erythrocyte sedimentation rate; ANA=Antinuclear antibody; Anti-ds DNA=Anti-double-stranded DNA; USG=Ultrasonography; RT-PCR=Real-time polymerase chain reaction; SGOT=Serum glutamic-oxaloacetic transaminase; SGPT=Serum glutamic-pyruvic transaminase

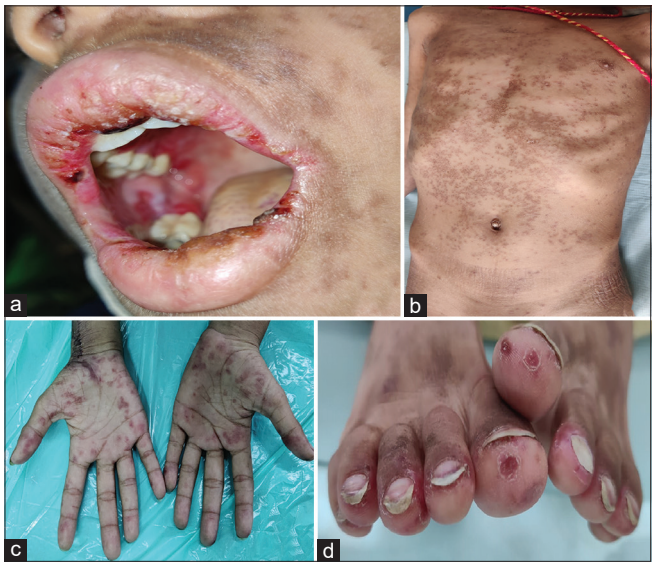

Figure 1: Pretreatment images of the patient. Erythematous maculopapular rash over the face and multiple ulcers and crusted erosions over the lips and oral mucosa (a), dusky erythematous maculopapular rash over the trunk (b), erythematous macules and papules over the palms (c), and erythematous papules over the soles (d)

He was managed with tablet hydroxychloroquine 50 mg BD and oral prednisolone syrup starting at 10 mg/day with gradual tapering, oral cetirizine 10 mg once a day, sunscreen lotion on sun-exposed areas, mometasone cream for skin lesions, and care of oral ulcers.

There was gradual improvement in the condition with disappearance of fever in 5 days postadmission, improvement in the skin rash and oral ulcers, and improvement in appetite with liver function normalizing (SGOT-89 U/L, SGPT-30 U/L). Thereafter, he was administered revised ART in the form of tablets zidovudine, lamivudine, lopinavir, and ritonavir. Significant improvement was observed with marked clearance of skin lesions, oral ulcers, and no fresh complaints at 3 months of follow-up [Figure 3]. CD4 count repeated after 3 months of revised ART was 195 cells/cmm. Tablet hydroxychloroquine was gradually withdrawn after 6 months. The patient had remained completely asymptomatic and is tolerating revised ART well at 2 years of follow-up.

Discussion

Lupus erythematosus is an autoimmune multisystem inflammatory disease associated with significant morbidity, mortality, and poor quality of life. Childhood-onset systemic lupus erythematosus (cSLE) is the terminology commonly used when lupus commences in an individual <18 years of age.[1] One study reported a prevalence of 3.2/100,000 children.[2] cSLE has more severe disease compared to adults with higher prevalence of lupus nephritis, photosensitivity, neuropsychiatric, and mucocutaneous involvement. The first case of SLE in persons living with HIV was documented in 1988.[3] There are reported cases of DLE and SCLE in people living with HIV.[1-5] Both cutaneous lupus and HIV can have overlapping clinical features; for example, oral ulcers could be a manifestation of HIV infection, various viral and fungal opportunistic infections, nutritional deficiencies, and drug reactions. Similarly, the malar rash of acute lupus could simulate viral exanthem, drug rash, seborrheic dermatitis in HIV, and immune reconstitution syndrome.

HIV and SLE have contrasting pathogenesis with progressive crippling of the immune system and development of anti-HIV antibodies being the central event in HIV and development of autoimmunity with elevated ANA and anti-dsDNA being the key event in SLE. Recent studies indicate that anti-HIV antibodies exhibit autoreactivity potential.[6,7] These autoreactive antibodies may be responsible for autoimmune

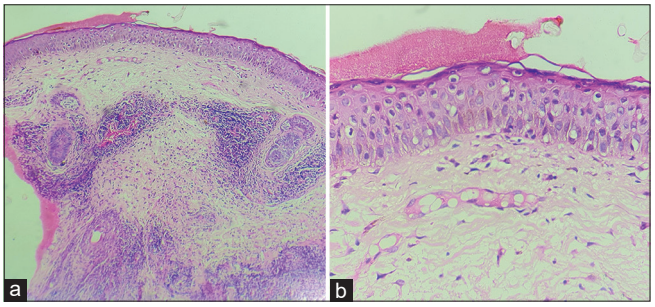

Figure 2: Skin biopsy Hematoxylin and Eosin stain (a) H and E, ×100; basal layer vacuolization and interface dermatitis, superficial perivascular, and perifollicular infiltrate composed of neutrophils and lymphocytes in the dermis, (b) H and E, ×400; interface dermatitis, superficial perivascular, and perifollicular infiltrate composed of neutrophils and lymphocytes in the dermis

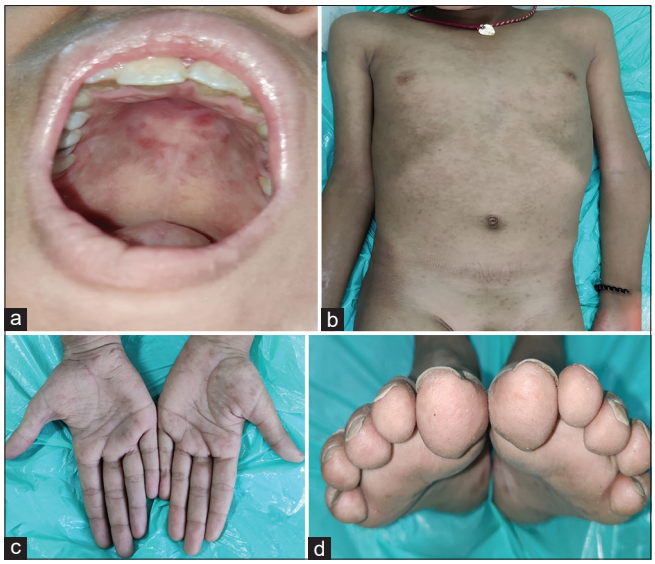

Figure 3: Posttreatment images of the patient. Resolved erythema and maculopapular rash over the face and clearance of oral mucosal lesions (a), postinflammatory hyperpigmentation after resolution of rash over the trunk (b), resolution of erythematous macules and papules over the palms (c), and resolution of erythematous papules over the soles (d)

phenomena. The autoantibodies in SLE may cross-react with HIV antigens giving rise to false positive anti-HIV antibody levels.[8,9] DILE is an adverse reaction to certain medications, whereby autoantibodies are formed after continuous drug exposure leading to an autoimmune disorder. It was first recognized in 1945 with sulfadiazine as the offending agent. Drugs causing DILE are procainamide, hydralazine, penicillamine, isoniazid, quinidine, antitumor necrosis factor inhibitors, interferon alpha, methyldopa, diltiazem, and chlorpromazine.[9]

The presentation of DILE depends on the type, frequency, and duration of the offending drug and may present as systemic lupus, subacute, or chronic cutaneous lupus.[9]

Reported patients of DILE have shown positive ANA antibodies with homogenous pattern, positive antihistone antibodies, and generally low or absent anti-double-stranded DNA antibodies.[10] There are no definitive diagnostic criteria for DILE, but the following guidelines have been proposed: (a) continuing exposure to a specific drug, (b) at least one symptom compatible with SLE, (c) no history suggestive of SLE before starting the drug, and (d) resolution of symptoms within weeks (sometimes months) after discontinuation of the offending agent.[11]

Our patient fulfilled all the criteria. He had no findings suggestive of lupus erythematosus before the initiation of ART, developed signs and symptoms 5 years after ART initiation, and his symptoms completely resolved on discontinuation of the offending drugs.

So far, there are two case reports of ART-induced DILE in persons living with HIV. In both the cases, diagnosis was established based on the clinical presentations, temporal association with ART introduction, and resolution of clinical symptoms on withdrawal of ART.[12,13] In one of the reports, emtricitabine, rilpivirine, and tenofovir were the offending drugs mentioned and the same were discontinued.[12] In the second report, ART was continued along with oral chloroquine, which led to clinical improvement.[13]

Conclusion

Drug-induced lupus, although extremely rare, should be considered a differential diagnosis in patients presenting with newer symptoms of skin rash and oral ulcers when on ART. Physicians need to closely follow-up patients and observe the evolution of rash and systemic involvement. SLE and HIV can coexist and further complicate the clinical scenario. Clinicopathological correlation and multidisciplinary involvement are essential in making an appropriate diagnosis and effective management of such cases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal patient identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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