Advanced human immunodeficiency virus (HIV) does not affect ability to utilize lymphadenopathy in assessment of drug reaction with eosinophilia and systemic symptoms syndrome in HIV and tuberculosis: Prospective comparative study

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Background: RegiSCAR validation criteria for drug reaction with eosinophilia and systemic symptoms (DRESS) includes lymphadenopathy, a frequent feature of both tuberculosis (TB) and human immunodeficiency virus (HIV). TB is the most common HIV-associated coinfection. Advanced HIV is associated with lymph node (LN) fibrosis. It is not clear if this negatively affects case validation in HIV-associated DRESS. To answer this question, we designed a prospective descriptive study to assess lymphadenopathy in various combinations of comorbid HIV, TB, and DRESS.

Objectives: We sought to describe the prevalence of DRESS-associated lymphadenopathy and characterize LN quality, size, and distribution in a high HIV-TB burden setting over time.

Methods: We prospectively and systematically examined LN in 25 consecutive acute DRESS cases hospitalized at a South African tertiary-care center and 10 hospitalized non-DRESS HIV-TB coinfected controls.

Results: Fourteen (56%) of 25 patients were HIV infected, with a median (interquartile range) CD4 count of 254 (66-478) cells/mm^3, and 7 of 14 were coinfected with TB. Using RegiSCAR criteria, 12 (46%) of 25 were definite DRESS cases, 8 (31%) of 25 probable, and 5 (23%) of 25 possible. Possible cases were excluded in the analysis. Fifteen (75%) of 20 subjects had LN in ≥2 anatomic sites, including all 7 patients with HIV-TB coinfection. In contrast, 1 (20%) of 5 hospitalized non-DRESS HIV-TB coinfected controls had LN. Cervical LN, in 15 (88%) of 17, was most common, followed by axillary (76%) and inguinal (59%). Cervical LN ranged between 1 and 2 cm in size. Among the 8 (32%) of 25 subjects with follow-up data, LN had regressed in all within 6 weeks of stopping the offending drug and initiating TB treatment. There was no correlation with CD4 cell count and LN.

Conclusion: Lymphadenopathy is a common feature of acute DRESS, even among HIV-TB–coinfected patients with advanced immunosuppression. (J Allergy Clin Immunol Global 2024;3:100276.)

Key words: *Lymphadenopathy, HIV, tuberculosis, DRESS syndrome, RegiSCAR diagnostic criteria*

Drug reaction with eosinophilia and systemic symptoms (DRESS) is an uncommon, potentially life-threatening, idiosyncratic reaction to a drug that is characterized by a rash with systemic features. It can arise anywhere between 2 and 8 weeks after drug initiation.[1] DRESS presents as a morbilliform eruption associated with fever, lymphadenopathy, and hematologic abnormalities, and it can affect multiple internal organs.[2] Lymphadenopathy, defined as lymph nodes (LNs) that are abnormal in size and consistency, is common in DRESS syndrome and is present in approximately 75% of cases.[3,4] A focal or generalized presentation of lymphadenopathy is associated with DRESS syndrome, with a predilection to cervical, axillary, and inguinal nodes; further, the affected nodes may be tender.[5,6] Criteria for case definition have been proposed by the Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) study group and the Japanese Research Committee on Severe Cutaneous Adverse Reaction. Lymphadenopathy in at least 2 sites is included in both diagnostic criteria.[7,8]

The RegiSCAR group has developed a diagnostic validation score, combining clinical and biological criteria for validation of potential DRESS cases. The score assigns each of the 8 major features a score ranging from −1 to 2 points, for a maximum score of 9 points. The certainty of diagnosis is based on the total score, as follows: <2 points, no case; 2-3 points, possible case; 4-5 points, probable case; and >5 points, definite case (see Table E1 in the Online Repository available at www.jaci-global.org).[7,9,10] In the score, lymphadenopathy carries 1 point, and if absent, 0 points. A single point has the potential to affect the certainty of the DRESS diagnosis. Lymphadenopathy together with eosinophilia,

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Abbreviations used
COVID-19: Coronavirus disease 2019
DRESS: Drug reaction with eosinophilia and systemic symptoms
HHV: Human herpesvirus
HIV: Human immunodeficiency virus
LN: Lymph node
RegiSCAR: Registry of Severe Cutaneous Adverse Reaction
TB: Tuberculosis

fever, and liver injury have been significantly associated with a "probable" or "definite" case of DRESS.[11]

During the latent phase of HIV infection, there is continuous depletion of lymphocytes and progressive involution of the germinal centers of LNs. Over time, the nodes become smaller or impalpable.[12,13] It has been suggested that the nonresolving adaptive responses in HIV result in collagen deposition and fibrosis of LNs.[14-17] However, it is not clear if this affects the detection of lymphadenopathy in HIV-associated DRESS. To answer this question, we decided to perform a prospective case–control study evaluating lymphadenopathy in HIV-infected and -uninfected patients with DRESS.

METHODS

In a single-blinded, case–control study conducted between September 2018 and November 2020, a total of 25 consecutive patients hospitalized for suspected acute DRESS and 10 hospitalized controls without DRESS were enrolled. All the controls were HIV infected, 5 were coinfected with tuberculosis (TB), and 5 were TB uninfected. Within 48 hours of admission, both patients and controls were clinically and systematically examined for lymphadenopathy by 2 independent clinicians unaware of the patients' HIV status, who reached consensus (Fig 1). For this study, LNs >1 cm diameter were considered clinically relevant, except for the epitrochlear, supraclavicular, popliteal, and iliac nodes, where the cutoff was smaller, at 0.5 cm.[18,19] Apart from presence and anatomic location, their size, character, and tenderness were recorded. Disagreements were settled by a senior clinician as the third reviewer. Six weeks after hospital discharge, all patients were recalled, and the LN examinations were repeated.

Using clinical photographs, histopathology, and clinical and laboratory data, all the cases clinically diagnosed as DRESS were categorized as definite, probable, possible, or no case using the validated diagnostic validation score developed by the RegiSCAR group (Table E1).[10] Only the cases validated as definite and probable were included in the analysis.

The study was conducted at Groote Schuur Hospital, a tertiary-care hospital in Cape Town, South Africa. It was approved by the human research ethics committee of the University of Cape Town. All participants provided written informed consent.

RESULTS

The demographic and clinical characteristics of the 25 possible patients with DRESS are summarized in Table I. The median (interquartile range) age was 38 (27-44) years, and most were female (64%). Twenty cases met the criteria for probable or definite DRESS and were included in the analysis. Thirteen (65%) of these 20 were HIV infected. Seven (54%) of those with HIV had advanced disease, and 7 (54%) were coinfected with TB. Three of those with HIV-TB coinfection (43%) had pulmonary TB, while the other 4 had disseminated disease. Fifteen (75%) of 20 had lymphadenopathy in more than one site. All HIV-infected patients had lymphadenopathy in at least one site; 12 (93%) of 13 had it in at least 2. HIV-TB coinfection (n = 7) guaranteed lymphadenopathy in at least 2 sites. This dropped to 43% (n = 7) in the HIV-uninfected cohort. All 3 patients (15%) without lymphadenopathy in the analysis were HIV uninfected (Table II).

Among the 17 cases of lymphadenopathy in at least one site, cervical nodes were the most affected (88%), followed by axillary (76%) and inguinal (59%). Among the 15 with lymphadenopathy in at least 2 sites, cervical and axillary nodes were found equally in 13 (87%) of 15 cases. All 7 patients with TB had lymphadenopathy in at least 2 sites, with all having axillary nodes and 6 of 7 cervical nodes. Inguinal nodes were found in 3 patients, 1 with pulmonary TB and 2 with extrapulmonary TB. The majority of LNs (60%), regardless of HIV status, were firm and rubbery. None of the patients had stony, hard LNs. The LNs mostly ranged between 1 and 2 cm in size (Tables II and III).

Five of the 10 controls were HIV-TB coinfected, while the other 5 were infected with only HIV. The demographic features of the controls are shown in Table IV. Two (20%) of 10 controls had lymphadenopathy in 2 or more sites, one each with TB and without active TB (Table V). The size and consistency of the LNs were similar to those of the cases. Table VI shows lymphadenopathy sites in control subjects based on TB infection.

DISCUSSION

To our knowledge, this is the first study to investigate the prevalence of lymphadenopathy in HIV-infected versus -uninfected patients with DRESS, with or without TB, 2 common coinfections—and both strongly associated with lymphadenopathy. Contrary to our hypothesis, we found that being HIV infected and having TB were additional risk factors for lymphadenopathy among DRESS cases, refuting the suggestion that lymphadenopathy is less prevalent in HIV infection. On the basis of our own experience and reports in the literature that fibrosis is a major feature in LNs in HIV infection,[14-17] we had hypothesized that DRESS patients with advanced HIV would be less likely to have lymphadenopathy. Ninety-three percent of DRESS patients infected with HIV had lymphadenopathy and met the threshold (≥2 sites) to add a point to the RegiSCAR validation score. Furthermore, among the DRESS cases without HIV or TB, 57% had single-site lymphadenopathy, while 43% had it recorded in at least 2 sites, further supporting lymphadenopathy as a feature of DRESS independent of an additional infective cause. One (20%) of 5 HIV-TB coinfected controls had lymphadenopathy in 2 or more sites. Similarly, only 1 (20%) of 5 HIV-infected subjects with no TB had lymphadenopathy in 2 or more sites, highlighting that HIV and TB do not always cause lymphadenopathy. However, it is not clear if the reported fibrosis of LNs in HIV affects their size, clinical characteristics, or functionality.

Among those infected with HIV, lymphadenopathy was recorded across CD4 count values, which ranged from 5 to 916 cells/μL. There seemed to be no correlation between the patient's CD4 count and lymphadenopathy. Unfortunately, virus loads, likely a better marker of HIV virus replication and ongoing

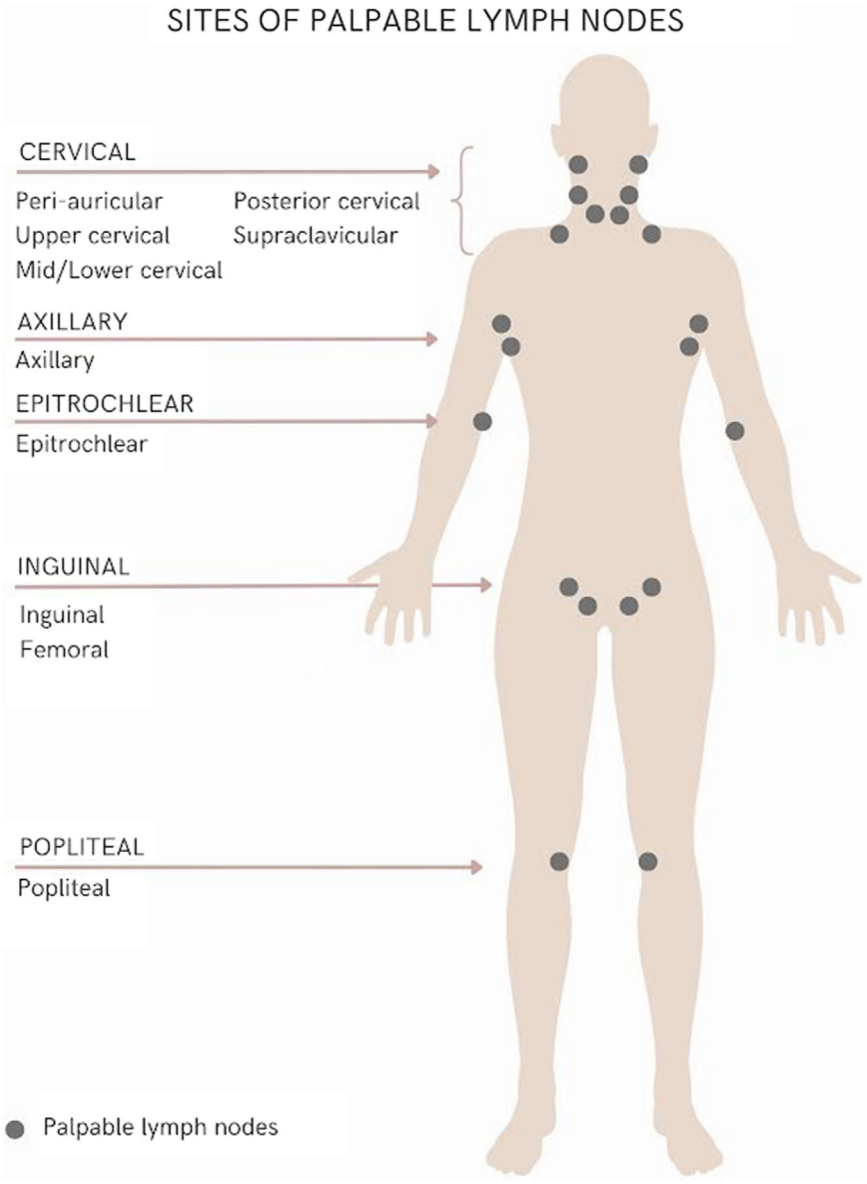

FIG 1. Palpable and nonpalpable LNs.

immune dysregulation, were not available for the majority of patients.

All patients with TB had lymphadenopathy in at least 2 sites, with all having axillary nodes and 6 of 7 also having cervical nodes. TB lymphadenopathy contributes up to 43% of peripheral LNs in TB-endemic settings, frequently presenting as chronic and nontender lymphadenopathy.[20] Cervical lymphadenopathy is a common presentation of extrapulmonary TB, reported in 63% to 77% of cases in contemporary series.[21-23] When considering all 3 (DRESS, HIV, and TB), 10 of 15 had both cervical and axillary involvement, with 8 having inguinal nodes. Compared to cases of DRESS and HIV, but not TB, 4 of 15 had cervical involvement, 3 of 15 had axillary involvement, and 5 of 15 had inguinal involvement. In the DRESS-only (no HIV or TB) subgroup, 3 of 15 had both cervical and axillary involvement, and only 2 had inguinal nodes. This suggests that in DRESS, the affected nodes are more generalized. The LNs were mostly 1 to 2 cm in size, with a firm and rubbery consistency. The inability to detect LNs <1 cm in size in this study supports previously published reports that the threshold for consistent palpability of LNs by experienced clinicians is 1.5 cm.[18]

Among the definite and probable DRESS cases, we found 75% to have lymphadenopathy that met the RegiSCAR criteria. This compares well, even the upper margins of previous studies that assessed lymphadenopathy in DRESS. A prospective RegiSCAR study of 117 probable or definite DRESS lymphadenopathy in 2 or more sites reported 54%.[7] A review of 130 probable and definite pediatric DRESS cases found 75% to have lymphadenopathy.[24] A Japanese study investigating the association of human herpesvirus (HHV)-6 reactivation with flares and severity of DRESS in 100 cases demonstrated that 71% of patients who had an increase in HHV-6 IgG titers had lymphadenopathy, while only 26% of those with no increase in HHV-6 IgG titers had lymphadenopathy.[25]

TABLE I. Demographic and clinical characteristics of 25 patients with possible DRESS

Characteristic	Value
No. of subjects	25
Age (years), median (IQR)	38 (27-44.5)
Sex	
Male	9/25 (36%)
Female	16/25 (64%)
HIV status	
HIV infected	14/25 (56%)
WHO clinical stage 3 and 4	7/14 (50%)
CD4 cell count (cells/mm^3), median (IQR)	253.5 (66-478)
HIV virus load	
Not assessed	2/10 (20%)
Undetectable	4/10 (40%)
Median (range) copies/mL	1050 (40-6989)
HIV uninfected	11/25 (44%)
TB	7/14 (50%)
Pulmonary TB	3/7 (43%)
Disseminated TB	4/7 (57%)
Comorbidity	
Hypertension	1/25 (4%)
Hepatitis B infection	1/25 (4%)
Epilepsy	1/25 (4%)
Asthma	1/25 (4%)
Gout	1/25 (4%)

IQR, Interquartile range; *WHO,* World Health Organization.

TABLE II. Lymphadenopathy assessment results according to HIV infection

Characteristic	All subjects	HIV infected	HIV-TB coinfected
No. of sites			
0	3/20 (15%)	0	0
1	2/20 (10%)	1/13 (8%)	0
2	9/20 (45%)	8/13 (62%)	5/7 (71%)
3	6/20 (30%)	4/13 (30%)	2/7 (29%)
LN characteristics			
Soft	5/20 (25%)	4/13 (31%)	2/7 (29%)
Firm and rubbery	12/20 (60%)	9/13 (69%)	5/7 (71%)
Stony hard	0	0	0
Site and size			
Cervical <1 cm	0	0	0
Cervical 1-2 cm	14/20 (70%)	10/13 (77%)	6/7
Cervical >2 cm	1/20 (5%)	1/13 (8%)	0
Axillary <1 cm	0	0	0
Axillary 1-2 cm	12/20 (60%)	9/13 (69%)	6/7
Axillary >2 cm	1/20 (5%)	1/13 (8%)	1/7
Inguinal <1 cm	0	0	0
Inguinal 1-2 cm	9/20 (45%)	7/13 (54%)	2/7
Inguinal >2 cm	1/20 (5%)	1/13 (8%)	1/7

Eight patients (32%) had information available for follow-up at 6 weeks, 6 of them HIV infected. Lymphadenopathy had resolved in all of them. The high dropout rate in the study was due to 2 in-hospital deaths and disruptions by the coronavirus disease 2019 (COVID-19) pandemic. This further supports the reactive ability of LNs in advanced HIV. However, the quality of this response in DRESS is not clear and needs further investigation.

The major limitation of this study is a high loss to follow-up due to the COVID-19 pandemic. The other limitations were small

TABLE III. Lymphadenopathy sites according to HIV infection

Site	All subjects	HIV infected	HIV uninfected	HIV-TB coinfected
Cervical only	2/17 (12%)	1/13 (8%)	1/4 (25%)	0
Axillary only	0	0	0	0
Inguinal only	0	0	0	0
Epitrochlear only	0	0	0	0
Popliteal only	0	0	0	0
Cervical + axillary	5/17 (29%)	4/13 (31%)	1/4 (25%)	4/7 (57%)
Cervical + inguinal	2/17 (12%)	2/13 (15%)	0	0
Axillary + Inguinal	2/17 (12%)	2/13 (15%)	0	1/7 (14%)
Cervical + axillary + inguinal	6/17 (35%)	4/13 (31%)	2/4 (50%)	2/7 (29%)

TABLE IV. Demographic and clinical characteristics of control subjects

Characteristic	Value
Age (years), median (IQR)	43.5 (38-46)
Sex	
Male	4/10 (40%)
Female	6/10 (60%)
HIV status	
HIV infected	10/10 (100%)
WHO clinical stage 3 and 4	5/10 (50%)
CD4 cell count (cells/mm^3), median (range)	201 (123-575)
TB	
Pulmonary TB	2/10 (20%)
Disseminated TB	3/10 (30%)
HIV-TB	5/10 (50%)
Comorbidity	
Diabetes mellitus	1/10 (10%)
Hepatitis B infection	1/10 (10%)
Cardiac failure	1/10 (10%)
Iron-deficiency anemia	1/10 (10%)
Granulomatous inflammation	1/10 (10%)

IQR, Interquartile range; *WHO,* World Health Organization.

sample size due to the relative rarity of DRESS and a paucity of pediatric cases. The only participant under the age of 18 years was 15 years old. Virus load, a marker for ongoing virus replication, was known in a small proportion of HIV-infected cases.

Conclusions

Contrary to our hypothesis, we found that being HIV infected and having TB were additional risk factors for lymphadenopathy among DRESS cases. Our study supported lymphadenopathy as an independent feature of DRESS. We found CD4 count, which we used as a proxy for World Health Organization stage of HIV, not to correlate of presence and quality of lymphadenopathy. Axillary, cervical, and inguinal nodes formed the majority of affected nodes in DRESS. Last, we established that DRESS-associated lymphadenopathy, even in the presence of treated TB and HIV, resolves with eliminating the offending drug and initiating TB treatment.

DISCLOSURE STATEMENT

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TABLE V. Lymphadenopathy frequency according to TB infections in control subjects

No. of sites	All patients	HIV, no TB	HIV-TB coinfected
0	7/10 (70%)	4/5 (80%)	3/5 (60%)
1	3/10 (30%)	1/5 (20%)	2/5 (40%)
2	2/10 (20%)	1/5 (20%)	1/5 (20%)
3	2/10 (20%)	1/5 (20%)	1/5 (20%)

TABLE VI. Lymphadenopathy sites according to TB infections in control subjects

Site	All patients	Pulmonary TB	Disseminated TB
Cervical	1/5 (20%)	1/2 (50%)	0
Axillary	0	0	0
Inguinal	0	0	0
Epitrochlear	0	0	0
Popliteal	0	0	0
Cervical + axillary	0	0	0
Cervical + inguinal	0	0	0
Axillary + Inguinal	0	0	0
Cervical + axillary + inguinal	1/5 (20%)	0	1/3 (33%)

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