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CASE REPORT

Lymphoproliferative skin lesion as a previously unreported adverse event detected in a patient receiving mSTR TB treatment

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ABSTRACT

Case Presentation: This case report presents an unreported adverse event detected when conducting pharmacovigilance activity among the patients' cohort receiving short, modified, all-oral treatment regimens (mSTR) for rifampicin-resistant tuberculosis (TB). Lymphoproliferative skin lesion was diagnosed histologically.

Results: The withdrawal clinical response and re-challenge positive test were detected, and the causal relationship was defined as "probable".

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Introduction

The mSTR study evaluating the effectiveness and safety of modified all-oral shorter rifampicin resistant tuberculosis treatment regimens has been conducted in Armenia since August 2020. Pharmacovigilance is an integral part of the study and the evaluation of cumulative incidence rate of serious adverse events (SAE) and adverse events (AE) of grade 3 and greater is one of the study objectives.

The skin lesions characterized as drug-associated pseudolymphomas was described previously in the other publications (Margo *et al*., 1996). No similar cases related to second-line tuberculosis drugs were found in the literature sources and AE databases available to us.

Case description

The patient was a 64-year-old man who received mSTR treatment (Bedaquiline (Bdq), Levofloxacin (Lfx),

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Linezolide (Lzd), Clofazimine (Cfz), Cycloserine (Cs)) for Pulmonary Tuberculosis initiated from June 2021. The patient was adherent to the treatment. TB treatment was effective, evidenced by the sputum culture conversion from the first treatment month and positive X-ray dynamics.

Lfx was stopped after three weeks of therapy and replaced by Moxifloxacin (Mfx) on Feb 07, 2021 because of arthralgia.

The manifestation of the AE took place after two and half months from TB treatment start and initially was identified as "Skin Hyperkeratosis". The skin on the trunk, upper and lower extremities was affected. As such conditions were generally attributed to Cfz, the drug was suspended, but no positive dynamics was registered after two weeks of Cfz suspension. That is why, the whole TB treatment was suspended for more two weeks. After this short treatment suspension, the skin condition slightly improved.

TB treatment (Bdq Mfx Lzd Cs) was re-initiated without Cfz which remained withdrawn permanently not to exacerbate the skin hyperkeratosis. The AE progressed after re-initiation of the drugs. The skin of the head and face was involved also. The lesion of the skin was expressed by dryness, scaling, thickening and colour change to brown and dark purple. The patient was complaining of itching on the all affected area. Flumetasone cream and cetirizine were administered, but the treatment was not effective.

Skin biopsy and histological examination was carried out. The histological examination revealed: lymphoproliferative skin lesion (Mycosis fungoides?).

The definite diagnosis was not revealed even by histochemical examination. In the result of the histochemical examination it was concluded that the changes in the examined sample were more characteristic for Cutaneous T-cell Lymphoma (Mycosis fungoides), but there was necessity to conduct polymerase chain reaction clonal test (not available in Armenia) for T-lymphocytes to clarify the diagnosis. According to the specialist conducting the histochemical examination the revealed cell infiltrate might also be the result of drug induced dermatosis. This has been presented in **Figure 1**.

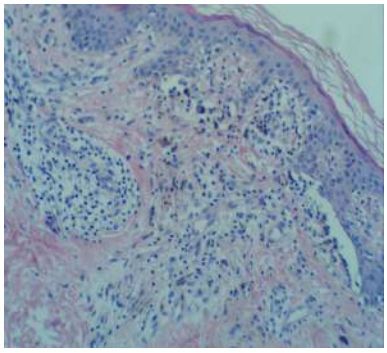

Figure 1a, 200 magnification, H&E stain

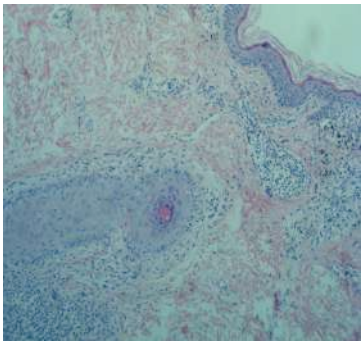

Figure 1b, 100 magnification, H&E stain

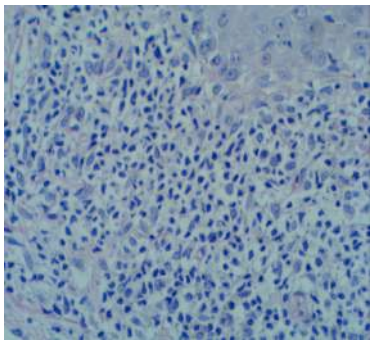

Figure 1c, 400 magnification, H&E stain

Figure 1. The histological images of the skin sample obtained from the patient with lymphoproliferative skin lesion

The cell pattern described in the examined sample was the following: CD3 + expression in the big number of T-lymphocytes, CD4+ expression in the majority of T-lymphocytes, CD5+ expression in the majority of CD3+ T-lymphocytes, CD8+ expression in 30% of CD3 T-lymphocytes, CD30+ expression in the several big cells, CD20+ expression in the moderate quantity of B-lymphocytes, CD68+ expression in the tissue-resident macrophages. This has been presented in **Figure 2.**

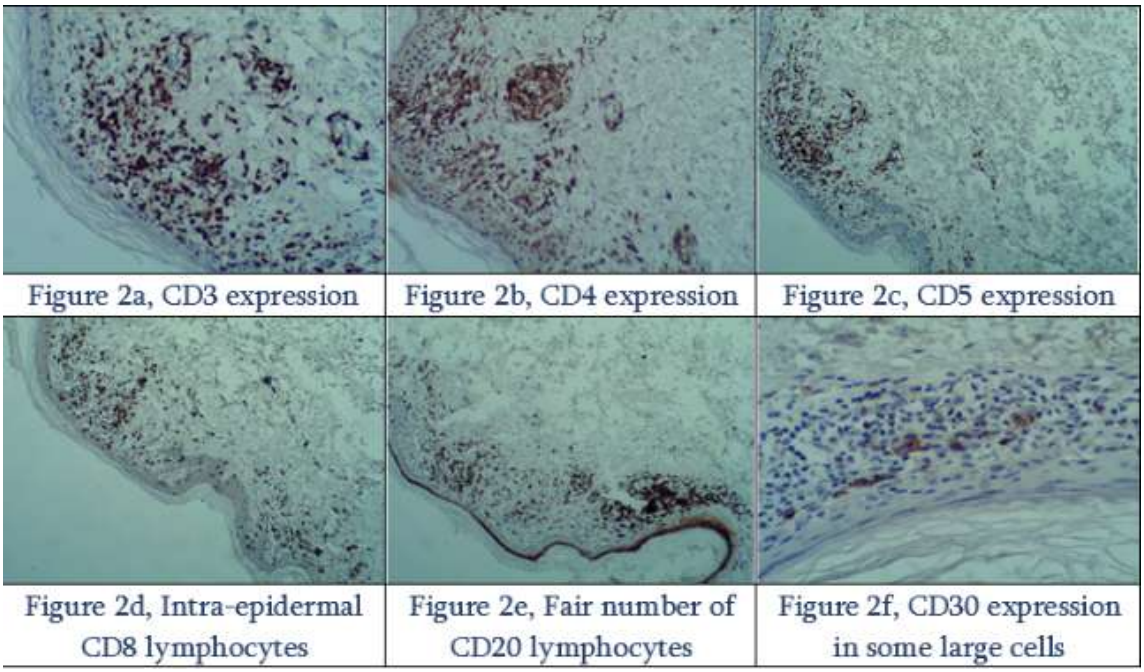

Figure 2. The histological images of the cell pattern in the skin sample obtained from the patient with lymphoproliferative skin lesion

It is worth to mention, that the increased CD3+ expression as a histochemical sign of the drug induced dermatosis had been reported previously (Novice *et al*., 2020).

It is also important to notify that no other clinical and laboratory findings were detected to confirm the diagnosis of Cutaneous T-cell Lymphoma. No splenomegaly or lymphatic node enlargement was revealed by ultrasonography. The blood count was within the normal ranges.

Taking into account the aforementioned, it was decided not to exclude the drug induced dermatosis and to stop TB treatment for a longer period compared with the previous suspension. The whole TB treatment was stopped for the second time in December 2021. The significant positive dynamics of the skin condition (decrease of hyperkeratosis and color recovery) and clinical signs (cessation of itching) were observed after a month from the TB treatment suspension. The Drug Resistant TB Consilium decided not to restart TB treatment, and the case outcome was declared as "failed treatment". The decision was made taking into account the evident positive dynamics of the skin condition after the treatment suspension and the high possibility of deterioration in case of restarting the second-line TB drugs.

Causality analysis

The causality assessment was conducted according to the "World Health Organization-Uppsala Monitoring Center system for standardized case causality assessment" (WHO, 2013).

The withdrawal clinical response was absent for Cfz, as when conducting the treatment without Cfz the AE didn't diminish and progressed, but withdrawal clinical response was detected twice related to the other TB drugs (Bdq Mfx Lzd Cs). For the first time, slight improvement was observed after the short treatment suspension in September 2021. The next de-challenge positive response was expressed by more significant improvement registered after the treatment stop in December 2021. The positive re-challenge test was detected for the abovementioned drugs (Bdq Mfx Lzd Cs), too.

Confounding factors related to the family history or other drugs weren't identified. Although the patient received concomitant drugs, no reasonable relationship between them and the AE was observed. The drugs administered for arthralgia (Ibuprofen, Tolperisone and Meloxicam) had been stopped two weeks earlier of the AE manifestation date. The improvement of the skin condition was observed when TB treatment was stopped but the patient was receiving Tamsulosin.

Conclusion

Based on the causality analysis, the causal relationship between the AE and following drugs (Bdq Mfx Lzd Cs) was estimated as "probable". The AE was reported as a SAE and entered in the study and pharmacovigilance databases.

Conflict of interest

There are no conflicts of interest related to this manuscript.

Abbreviations

mSTR: Modified Short Treatment Regimens

AE Adverse Event

SAE: Serious Adverse Event

TB: Tuberculosis

Bdq: Bedaquiline

Lzd: Linezolide

Lfx: Levofloxacin

Mfx: Moxifloxacin

Cs: Cycloserine

Cfz: Clofazimine

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