

CASE REPORT

Lymphocyte transformation test: The multiple positive results turned to all negative after influenza infection

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Abstract

Previously positive lymphocyte transformation test (LTT) results changed to negative during influenza infection. As observed in the current article, results of LTT may be influenced by infection; therefore, it is crucial to consider the timing of LTT.

KEYWORDS

DLST, influenza, lymphocyte transformation test, Th1, Th2

1 | INTRODUCTION

A middle-aged woman suffered from drug reaction. Lymphocyte transformation test (LTT) was performed for her suspected medicine, and results showed all positive. When she developed influenza, results of LTT turned to all negative. Her immune reaction against multiple drugs might change to negative due to Th2-to-Th1 conversion by influenza infection.

Lymphocyte transformation test is often performed as a method for the diagnosis of drug eruption. The method is simple and low risk for the patient suspect for drug eruption. However, it is possible to be a false positive. The phenomena observed in LTT as a proliferative response of T cell lymphocytes do not always correspond directly to the allergic reaction occurring in vivo of the patient. The results of LTT may produce misleading by depending on patient's condition. Also, the results of LTT vary depending on the drug. False-positive rates of LTT are higher when the drug itself stimulates lymphocyte proliferation.¹⁻⁶ Th1 cells proliferate in the presence of infection. The positive rate of LTT varies depending on the type of drug eruption, too.⁷⁻⁹ LTT is a simple in vitro system, and its use requires

accurate interpretation due to its simplicity. However, there is no doubt that LTT is a study that can provide useful information in situations where a drug challenge test (DCT) is difficult to conduct.

2 | CASE PRESENTATION

A 37-year-old woman with no past medical history suffered from asymptomatic and repeated eruptions consisting of diffuse and fused purpura on whole body for 6 months. At the time of first visit to Mie university hospital, although the eruptions did not appear, she was suspected that she might have developed drug-associated eruptions based on her medical history including non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, alprazolam, and others. Whole blood count and laboratory examination including inflammatory markers were within the normal range, and the results of IgE-RAST for common allergens were also undetected. Computed tomography (CT) finding for whole body was without any abnormalities. Therefore, the possibility of her skin rashes associated with infections, other allergic reactions, and malignancies was excluded. Then,

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the LTT for the suspected drugs was performed (BML Inc.). The results were all positive (Table 1, 1 year before), and then she was advised to discontinue the tested drugs except for alprazolam. The eruptions did not reoccur; however, after 1 year she visited Mie university hospital again and she requested to identify drugs that would be safe for her to take. The LTT was performed again for all the present and previously prescribed drugs. The results of the LTT were again all positive (1 month before). She was required to undergo DCT to support the results of the LTT. She hospitalized in premise to perform DCT and immediately blood sample for LTT was taken. After 12 h of hospitalization, she developed a high fever and was diagnosed as having an influenza infection. Surprisingly, all the LTT results were negative for the suspected drugs (admission). Eleven days after recovering from the influenza infection, LTT was performed for the same drugs. Some of the LTT data had turned positive (11 days later). Patch test was performed at the concentration of 10% and 20% dilution degree for the same drugs tested in LTT. The test results were all negative. Finally, DCT for tiaramide and loxoprofen was performed; however, eruptions did not reoccur. The DCT for acetaminophen was not performed owing to its high-level stimulation index (SI) in LTT. She took care not to take acetaminophen and no recurrence of the skin rash was observed.

3 | DISCUSSION

This is a rare case showing sequential LTT results; multiple positive results transiently changed to all negative

TABLE 1 Sequential LTT results

LTT S.I.	1 year before	1 month before	At admission	11 days later
Acetaminophen	7.9	6.6	1.7	13.1
Ibuprofen	6.5	N.T.	N.T.	N.T.
Loxoprofen	7.2	8.7	1.2	5.3
Alprazolam	3.9	3.2	1.3	5.3
antiflatulent	8.2	14.8	N.T.	N.T.
Tiaramide	N.T.	N.T.	1.1	1.4
Aspirin	N.T.	N.T.	1.3	1.5
BCG vaccine	N.T.	N.T.	139.9	138.4
cpm of control	387819	134958	116942	92236

Note: Lymphocyte transformation test (LTT); Stimulation index (S.I.); Not Tested (N.T.); S.I. > 1.8: positive, 1.6 ≥ S.I. < 1.8: false positive, S.I. < 1.6: negative; 1 year before: internal use of some drugs; 1 month before: internal use of only alprazolam; At admission: at that time of influenza virus infection; 11 days later: after recovery from influenza; BCG measured for positive control; Triamide and aspirin were tested to look for alternative medications.

during influenza infection. LTT is useful for the diagnosis of drug-induced reactions. LTT reveals the proliferation of T-cells, which is measured by a 3H-thymidine uptake via simulation by the targeted drug in vitro. The positive rate for LTT is not perfect, for example β-lactam allergy is in the range of 60%–70%.⁶ If there are many lymphocytes sensitized by the drug present in the blood, it tends to be positive. Therefore, the result of LTT is more likely to be positive in severe drug eruptions at early stage.^{7,8} In this point, LTT is very useful in the diagnosis of severe drug eruptions. However, in case the results of LTT are positive for multiple drugs, the reliability is not always high. Anti-tumor and immunosuppressive drugs, vancomycin, and herb medicine may directly stimulate lymphocytes and affect the proliferative capacity of white blood cells (WBC).^{1–5} Some NSAIDs enhance proliferation, which is normally explained by their ability to inhibit PGE2 synthesis.⁶ The other hand, in case of pseudo-lymphoma and erythroderma papulosum types of drug eruptions, there may be many Th2 cells in the blood, and therefore LTT is more likely to be positive and SI levels are higher.⁹ The discrepancy of the results between the patch tests and LTT may occur, because the drugs do not sufficiently penetrate through the cornified layer of the epidermis.⁹ There was no correlation between a positivity of LTT and patch test.

In the current case, the patient was taking only alprazolam when final LTT was performed. How did the influenza infection relate to negative change of LTT results? Total WBC count and lymphocyte count were unchanged. The lymphocyte bioactivity seemed to be unchanged because of the data for count per minute without stimulation (Table 1). Since the patient's drug eruption type was similar to erythroderma papulosum, the activated Th2 cells might exist in the blood. The other hands, infection such as influenza virus induces a Th1 response.¹⁰ Immune reaction might shift to Th2 by the current tested drugs in LTT, which changed to negative due to Th1 conversion by the influenza infection. It is important to consider the appropriate timing to perform LTT.

4 | CONCLUSION

The immune reaction against tested drugs had changed to negative due to Th2 to Th1 conversion during influenza infection. It is important to consider the appropriate timing to perform lymphocyte transformation test, because immune reaction might be influenced by infection.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

MK and SI treated the patient. MK, AU, TN, KH and KY wrote the manuscript.

DATA AVAILABILITY STATEMENT

The patients data is not publicly available on legal or ethical grounds.

CONSENT

All the mentioned authors consent for publication. Written consent was obtained from the patient.

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