

# Highlights: Focus on immunodeficiency-associated lymphoproliferative disorders

Commentary

## Current topics on other iatrogenic immunodeficiency-associated lymphoproliferative disorders and EBV-positive mucocutaneous ulcer

Yasuharu Sato

**Keywords:** Immunodeficiency-associated LPD, immunosuppressive drugs, MTX, EBV-positive mucocutaneous ulcer, spontaneous regression.

Methotrexate (MTX) was the first reported immunosuppressive agent associated with lymphoproliferative disorders (LPD) or lymphomas, predominantly in patients being treated for rheumatoid arthritis (RA). Additionally, LPD also develop in immunodeficient patients being treated with MTX; these LPD were defined as MTX-associated LPD in the World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues 3<sup>rd</sup> ed. (2001).<sup>1</sup> However, immunodeficiency-associated LPD also develop in patients receiving other immunosuppressive drugs such as biologics, tacrolimus, and non-tacrolimus immunosuppressants. Thus, in the WHO classification 4<sup>th</sup> ed (2008), 'MTX-associated LPD' was changed to 'Other iatrogenic immunodeficiency-associated lymphoproliferative disorders (Oii-LPD)'.<sup>2</sup>

Immunosuppressed patients who are treated using immunosuppressive drugs for an underlying primary disease subsequently develop Oii-LPD. The most common primary disease is RA, followed by dermatomyositis, psoriasis, psoriatic arthritis, systemic lupus erythematosus, and inflammatory bowel disease (IBD). Additionally, according to a published paper, the risk factors associated with Oii-LPD onset in Japan are the use of methotrexate or tacrolimus and higher age.<sup>3</sup>

The WHO classification does not clearly indicate the category of histological subtypes; however, the framework of subtype classification is similar to that of the classification of post-transplant LPD, and recent studies have attempted to subcategorize Oii-LPD to fit into this unique disease type.

In this review series, the authors provide an overview of the Oii-LPD with respect to their histopathological findings, immunophenotype, genetics, clinical behaviors, and clinical management.

Most Oii-LPDs are of B-cell lineage such as diffuse large B-cell lymphoma-type (35%), classic Hodgkin lymphoma-type (25%), or classic Hodgkin lymphoma-like lesions (8%), with cases of follicular lymphoma being less common. Momose *et al.* previously described the clinicopathological and genetic features of B-cell type Oii-LPD.

T- or NK-cell type Oii-LPD are rare, and published case reports are limited. To clarify the clinicopathological findings and characteristics of T- or NK-cell type Oii-LPD, Satou *et al.* focused on MTX-associated T-LPD, MTX-associated NK/T-LPD, and hepatosplenic T-cell lymphoma in patients with IBD.

Epstein-Barr virus (EBV)-positive mucocutaneous ulcers were first described as a lymphoproliferative disorder in 2010 and were classified in the WHO classification revised 4<sup>th</sup> ed (2017) as a specific type of Oii-LPD.<sup>4</sup> Ikeda *et al.* reviewed the reported cases of EBV-positive mucocutaneous ulcers, focusing on their clinical and pathological aspects as compared with those of other EBV-positive B-cell neoplasms.

The clinical management for Oii-LPD is not established, and the prognosis of each histological subtype is unclear, excluding the classic Hodgkin lymphoma-type. Classic Hodgkin lymphoma-type does not exhibit remission with MTX discontinuation alone and requires additional chemother-


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Division of Pathophysiology, Okayama University Graduate School of Health Sciences, Okayama, Japan.

**Corresponding author:** Prof. Yasuharu Sato, Division of Pathophysiology, Okayama University Graduate School of Health Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan. E-mail: satou-y@okayama-u.ac.jp

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apy.<sup>5</sup> Tokuhira *et al.* summarized the prognosis of each histological subtype and their clinical management.

A significant proportion of patients with Oii-LPD demonstrate partial or complete regression in response to the withdrawal of immunosuppressive drugs. Although the reason is unclear, recent studies suggest that the early recovery of the absolute lymphocyte count after withdrawal of MTX is associated with the spontaneous regression of MTX-associated LPD. Saito *et al.* summarized the immune response in patients with Oii-LPD, and discussed the relationship between prognosis and absolute lymphocyte count (this review article will be published in the next issue).

All reviews reflect the past to present knowledge of Oii-LPD, and are expected to help clinicians, pathologists, and researchers.

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