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Journal of Cellular Immunology Short Communication

Juvenile-onset Systemic Lupus Erythematosus Accompanied by Secondary Thrombotic Microangiopathy

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Received date: July 23, 2020 , **Accepted date:** August 17, 2020

Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple organ systems. Juvenile-onset SLE (jSLE) accounts for up to 20% of all SLE patients. Compared to adult-onset SLE, jSLE patients tend to show different manifestations of SLE and are often difficult to diagnose promptly. JSLE patients show severe disease conditions, and intensive treatments are therefore required to control disease activity. Thrombotic microangiopathy (TMA) is defined as a condition with vascular damage due to microvascular obstruction and endothelial cell injury. TMA is diagnosed through clinical features and pathological findings; clinical features include microangiopathic hemolytic anemia, thrombocytopenia, and multiple organ injury. Secondary TMA is associated with various causes such as drugs, organ transplants, and autoimmune diseases. SLE is one of the most common immune disorders accompanied by TMA, and the condition of the patients are usually severe. Although TMA occurring in jSLE patients is rare, it can be life-threatening. Because there are only a few reports of jSLE cases accompanied by secondary TMA, it is important to accumulate the data of each case. In this article, we would like to discuss the mechanisms of secondary TMA with jSLE and the treatment strategy, that we learned from our experience and previously reported cases. Combination therapy including immunosuppressants and plasma exchange is needed to control disease activity; in particular, suppressing complement pathways is important. Novel therapies such as eculizumab, rituximab, and belimumab require more data to determine whether they are effective in cases of TMA with SLE. The establishment of a treatment strategy based on evidence is needed for jSLE accompanied by TMA. The possibility of jSLE patients having a gene mutation, when they are resistant to treatment or when disease onset is at a young age, means we should consider performing gene analysis for those patients.

Keywords: Juvenile systemic lupus erythematosus, Thrombotic microangiopathy, Life-threatening, Complement cascades, Gene mutation

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple organ systems. Juvenile-onset SLE (jSLE)—also called childhood-onset SLE—is usually defined as SLE with disease-onset before the 18th birthday. Patients with jSLE are reported to account for up to 20% of all SLE patients [1,2]. The estimated incidence of jSLE is between 0.36 and 2.5 per 100,000 children [1,3,4], which is much lower than that of adult-onset SLE: 1 to 25 per 100,000 [5,6]. The clinical features of jSLE tend to differ from those of adult-onset SLE, which is one of the reasons why defining diagnosis is sometimes difficult in jSLE patients. The classification criteria of the American College of Rheumatology (ACR-1997) [7], in worldwide use, consist of clinical features criteria and laboratory abnormalities criteria. The ACR-1997 shows 89.6% sensitivity and 98.1% specificity in adult-onset SLE, compared to 84.3% sensitivity and 94.1% specificity in jSLE. This reduced sensitivity is because the symptoms that develop in jSLE at the onset are usually partially those that develop in adult-onset SLE patients. The Systemic Lupus International Collaborating Clinics classification criteria (SLICC-2012) [8], which was established because of

concerns regarding sensitivity and shows 94.6% sensitivity and 95.5% specificity in adult-onset SLE, shows sensitivity as high as 99.6% in jSLE; however, specificity drops to 82.0% [9]. Although we must wait for verification of the utility of the ACR/European League Against Rheumatism (EULAR) 2019 criteria [10], these figures indicate that precise diagnosis in jSLE patients is difficult. JSLE and adult-onset SLE patients differ not only in terms of clinical symptoms. Some reports describe the disease severity of jSLE patients compared to adult-onset SLE patients [11-14]. For example, jSLE patients are reported to have more severe organ involvement and a higher mortality ratio; as high as 18.3 in standardized mortality ratio, which is much higher than the value of 3.1 reported in adult-onset SLE [15]. Moreover, as in other child-onset critical systemic disease patients, jSLE patients must live with their disease for a far longer time than most adult-onset SLE patients do; thus, they have a much greater risk of developing organ dysfunction caused by the disease itself and by the side effects of medications. Therefore, our treatment aim is to control disease activity by sufficient induction therapy as soon as possible and ensure the minimum required maintenance therapy.

Thrombotic microangiopathy (TMA) is a condition of vascular damage due to microvascular obstruction and endothelial cell injury [16]. TMA is diagnosed through clinical features and pathological findings [17]. Clinical features include microangiopathic hemolytic anemia, thrombocytopenia, and multiple organ injury [16,18]. Primary TMA occurs in complement disorders, e.g., atypical hemolytic uremic syndrome and ADAMTS13 deficiency, whereas secondary TMA is associated with various causes such as drugs, organ transplants, and autoimmune diseases. The incidence of secondary TMA in autoimmune diseases varies from 8-15%, depending on the diagnosed disease [19]. SLE is one of the most common immune disorders that is accompanied by TMA. One study of the Japanese TMA registry reported that the proportion of autoimmune diseases (defined in the study as connective tissue diseases and their allied diseases) amongst TMA cases was 24% (221/919) [20]. This makes autoimmune diseases the most frequent cause of secondary TMA, with SLE accounting for 41.6% of cases (92/221) [20]. On the other hand, the incidence of TMA in SLE patients in previous reports varies from 0.5-10.0%. [21-23]. Even though the reported incidence of TMA in SLE patients is inconsistent, every report describes the disease condition as very severe and life-threatening, and requiring intensive treatment including a combination of immunosuppressants and plasma exchange. Thus, it is important to make a prompt diagnosis in patients where SLE is complicated with TMA.

Juvenile-onset SLE accompanied by TMA is very rare; however, it is reported to be life-threatening, as is the case in adult-onset SLE [24]. Because there are only a few reports of jSLE cases accompanied by secondary TMA, it is important to accumulate the data of each case. We have recently reported a pediatric case of refractory jSLE accompanied by TMA [25]. The patient was a 5-year-old girl who presented to a hospital complaining of fever, edema, and diarrhea, and was found to have hypertension and pleural effusions. Blood and urine examinations revealed that she had renal dysfunction, thrombocytopenia, hemolytic anemia, nephrotic syndrome, hypocomplementemia, and elevated anti-dsDNA IgG levels. The result of an antiphospholipid antibody test was negative and there was no decrease in ADAMTS13 activity. We diagnosed her with SLE, according to the ACR-1997 classification criteria, accompanied by TMA, which was confirmed by the histological study of a renal biopsy specimen. Her disease condition was very severe and refractory. Combination therapy involving methylprednisolone pulse therapy (MPT), mycophenolate mofetil (MMF), and plasma exchange (PE) was effective but insufficient. Eculizumab could not control disease activity of either SLE or TMA, although it contributed to raising platelet count. We administered a series of intravenous cyclophosphamide therapy (IVCY) courses, in addition to MPT and PE, and we finally controlled disease activity after 28 PEs, 8 MPT courses, and 9 IVCY courses. She had been suffering from severe complications, mostly caused by steroids; however, she recovered dramatically after the disease activity was controlled. She is now about one and a half year after induction treatment completion, and she continued medication of PSL, MMF, and hydroxychloroquine, and going to school by herself. Naturally, we must follow her up very carefully to monitor the flare and organ dysfunctions, especially regarding kidney involvement.

TMA in SLE patients can occur by several mechanisms, such as dysregulation of the complement system and the activation of antiphospholipid antibodies [26,27]. Antiphospholipid antibodies cause coagulation mechanism activation, vascular endothelial injury, and activation of the complement system, leading to thrombus formation [27]. Moreover, infection and stress can trigger the acceleration of thrombus formation [28]. Dysregulation of the complement system is the most pivotal factor in developing TMA in SLE. Some reports describe that the activation of classical pathways plays a key role in the pathogenesis of TMA with SLE [29,30]. Furthermore, some studies report that the activation of the alternate pathway exists in TMA in parallel with SLE flares, as well as the activation of the classical pathway of TMA with SLE [31,32]. Thus, we can assume that controlling the disease activity of TMA with SLE requires not only the suppression of one complement factor but whole complement cascades. The combination treatment that is

proven to be effective for severe SLE—namely MPT, MMF, IVCY, and hydroxychloroquine—should be used promptly together with PE to suppress abnormal immune activity and complement activation. We administered eculizumab in addition to the combination therapy, having presumed that it could prevent thrombus formation derived from C5a, but it failed to control the disease activity of either TMA or SLE (although it did succeed in raising the platelet count). Even though some reports show the efficacy of eculizumab for patients of TMA with SLE [33,34], we must wait for sufficient data and indications, because the side effects of severe infection, especially by meningococcus, could be fatal. Other therapeutic options include rituximab and belimumab, biologics that affect B cell function. Rituximab is reported to be effective for TMA accompanied with SLE [22]; however, supporting data is limited and further study is needed to judge the effect. Belimumab is a novel therapeutic agent for SLE [35], but we still have to wait for the results of a trial.

There is one further issue that requires attention. When an SLE patient develops TMA, especially when that patient is resistant to treatment, we must confirm whether there is a gene mutation that is involved in complement-regulatory genes. There are reports that treatment-resistant TMA patients with SLE had gene mutations [21,36]; one report showed 6 out of 10 patients had mutations associated with atypical hemolytic uremic syndrome, although it concerned adult-onset SLE [36]. Treatment options may change for such patients, and as such we should perform gene analysis promptly. As far as gene mutations, we should highlight that jSLE patients, especially when the age of onset is young, may have a gene mutation associated with the development of SLE. A group of immunological pathway disorders caused by a single gene mutation has been shown to develop the same pathological condition as SLE, for example: type I interferonopathy caused by *ACP5* mutation, auto-antigen excess caused by *DNASE1* mutation and *DNASE1L3* mutation, and tolerance caused by *TNFSF6* mutation, *PRKCD* mutation, and *IKZF1* mutation [37,38]. We should monitor carefully to identify other disease feature signs that can develop via these disorders and perform gene analysis accordingly.

The disease activity of juvenile-onset SLE can be very severe, especially when the patient develops TMA. We have to perform intensive treatment and consider the possibility of the patient having a gene mutation that is involved in either the onset of SLE or the onset of TMA. Establishing a treatment strategy is important in patients with jSLE accompanied by TMA.

Conflicts of Interest

The authors declare no conflicts of interest associated with this manuscript.

Funding Statement

Masaaki Mori receives funds from Nippon Kayaku Co.,Ltd., Asahi Kasei Pharma Co., AbbVie GK, Mitsubishi Tanabe Pharma Co.

Acknowledgements

We thank Dr. Kohsuke Imai, an associate professor of Department of Community Pediatrics, Perinatal and Maternal Medicine, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, for performing whole-exome sequencing of genome analysis and immunological analysis.

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