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Review Article

P-glycoprotein Expressing-B cell associated Active True Renal Lupus Vasculitis in Lupus Nephritis

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ABSTRACT

True renal lupus vasculitis (TRLV), a rare form of vascular lesion usually associated with proliferative lupus nephritis (LN), is resistant to conventional treatments and associated with poor renal outcome among renal vasculopathies. Evidence suggests the involvement of P-glycoprotein (P-gp) expressing-activated B cells in the pathogenesis and treatment resistance of TRLV through the production of autoantibodies and direct infiltration into the inflammatory lesion of small vessels. Therapies targeting activated B cells might overcome refractory TRLV. Identification of the subsets of peripheral activated B cells that express P-gp in TRLV patients might help the selection of suitable treatment strategy.

Keywords: True renal lupus vasculitis; B cell; P-glycoprotein; Lupus nephritis

INTRODUCTION

Lupus nephritis (LN) often develops in patients with systemic lupus erythematosus (SLE) during the course of the disease [1]. The International Society of Nephrology and the Renal Pathology Society (ISN/RPS) 2003 classification [2], which focuses on glomerular lesions, provides useful pathologic information on the assessment of the severity and prognosis of LN and the selection of appropriate treatment strategy. However, the ISN/RPS 2003 criteria do not include any vascular lesions [2]. The incidence of renal vasculopathy in LN is high (maximum of approximately 82% in renal biopsy), furthermore, LN patients with renal vasculopathy have poor renal outcome [3, 4]. Appel et al. [5] described five morphologic forms of lupus vasculopathy, including uncomplicated vascular immune deposits, non-specific arteriosclerosis, non-inflammatory necrotizing vasculopathy, thrombotic microangiopathy, and true renal vasculitis. Among these LN vasculopathies, true renal lupus vasculitis (TRLV) is a rare form of fibrinoid necrotizing vasculitis, and patients with TRLV have poor renal outcome among those with renal vasculopathies [3,6,7]. Among the refractory mechanisms responsible for the poor renal outcome in LN patients, we reported previously that P-glycoprotein (P-gp), encoded by the multidrug resistance-1 (MDR-1) gene, causes drug resistance in patients with highly active SLE, including active LN [8-11]. Furthermore, we also reported a case of P-gp-expressing B cell-mediated active TRLV [12].

There are only a few reports on TRLV in the medical literature. Therefore, there is a need for more information on the pathogenesis, mechanisms of treatment resistance, and appropriate treatment strategy. Here, we discuss the importance of activated B-cells, particularly those that express P-gp, in the pathogenesis of TRLV, and propose the potential of treatments that can target activated B-cells in refractory patients with TRLV.

MORPHOLOGY OF TRLV

TRLV is characterized by transmural and extensive infiltration of the blood vessel wall with inflammatory cells (Figure 1A), such as lymphocytes, including plasma-cell compartments and CD19+ B cells, monocytes and neutrophils [6, 12, 13]. These lesions are often accompanied by fibrinoid necrosis and destruction of the elastic lamellae [6, 13-15]. These changes are indistinguishable from those in polyarteritis nodosa or microscopic polyangiitis. However, TRLV is fibrinoid necrotizing vasculitis lacking antineutrophil cytoplasmic autoantibodies, and is characterized by confinement of the lesions to small arteries whereas other fibrinoid necrotizing vasculitis, including ANCA-related vasculitis and polyarteritis nodosa, exhibit lesions that involve vessels of various sizes including small arteries. The immunofluorescent findings in TRLV include variable staining for fibrin and immunoglobulins or complement components are in general limited to small arteries [6, 13].

TRLV develops in patients with highly active SLE and is commonly associated with proliferative LN classified as class III or IV based on the WHO or ISN/RPS 2003 classification [3, 6, 7]. A renal biopsy

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performed in the early stage of SLE detects active TRLV with LN classified as ISN/RPS class I (Figure 1A).

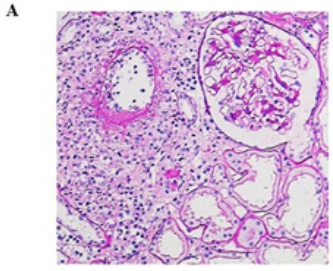

Figure 1A: True renal lupus vasculitis and P-glycoprotein expression on CD19+ cells. A. Histopathological findings in a patient with lupus nephritis complicated with true renal lupus vasculitis. Intralobular artery shows vasculitis with fibrinoid necrosis, inflammatory infiltrates, and destruction of the vascular wall. The glomerular lesion is classified as minimal mesangial lupus nephritis. (Periodic acid-Schiff stain, 100×).

In highly active SLE, TRLV can develop before progression to glomerular nephritis [12].

ROLE OF B CELLS IN TRLV PATHOGENESIS

The pathogenesis of TRLV parallels that of systemic lupus vasculitis [6].

B cells are involved in the pathogenesis of lupus vasculitis through:

- Production of autoantibodies, e.g., anti-endothelial cell antibodies (AECA) [16, 17], resulting in the formation of immune-complex, activation of the complement system and increased synthesis of cytokines in endothelial cells.
- Direct infiltration of activated B cells into the perivascular lesions of small blood vessels [12, 13, 18].

Among the autoantibodies in SLE, AECA levels are associated with the SLE disease activity index and also histopathological evidence of active lesions, including leukocyte infiltration and fibrinoid necrosis, in LN patients [19]. AECA antibody-associated cytotoxicity occurs uniquely in the presence of lymphocytes [20]. AECA may bind to endothelial cells and induce endothelial damage resulting in renal vasculopathy by complement activation, upregulation of adhesion molecules expression and enhanced production of cytokines including IL-6 in endothelial cells, promotion of leukocyte adhesion, induction of endothelial cell apoptosis and thrombosis [20-23].

Several groups have provided evidence for the existence of plasma-cell compartments and CD19+ B cells among the inflammatory cells infiltrating the blood vessel wall during the active phase of TRLV [6, 12, 13]. A representative patient with active TRLV showed expansion of peripheral P-gp+CD19+ B cells accompanied by marked accumulation of P-gp+CD19+ B cells at the site of TRLV inflammation (Figure 1B-D).

P-gp, which is the ABC transporter subfamily B member 1 (ABCB1), is a member of the ATP-binding cassette transporter superfamily and functions as an energy-dependent transmembrane efflux pump. Overexpression of P-gp on B cells leads to a reduction in intracellular concentrations of various drugs of P-gp substrates (Table), including corticosteroids, and results in the development of P-gp-mediated multidrug resistance [8, 9, 24-26]. Certain cytokines, such as IL-2 [9] and IL-6, can activate B cells and induce transcriptional activation of MDR-1, resulting in P-gp expression on B cells (Figure 2).

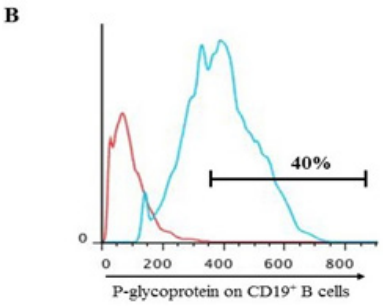

Figure 1B: True renal lupus vasculitis and P-glycoprotein expression on CD19+ cells. B. P-glycoprotein (P-gp) expression on peripheral CD19+ cells at the active phase of vasculitis (blue line) in the same patient shown in 1A, C and D. Red: isotype-control FITC-conjugated anti-mouse IgG Ab. Data represent the percentages of P-gp-positively stained CD19+ cells. The specific antibodies for staining and flow cytometric analysis were as follows: staining for P-gp using MRK16 (a specific monoclonal Ab (mAb) against P-gp; Kyowa Medex, Tokyo) with FITC-conjugated goat anti-mouse IgG mAb (BD Biosciences Pharmingen), cy-chrome-conjugated CD19 mAb (BD Biosciences Pharmingen).

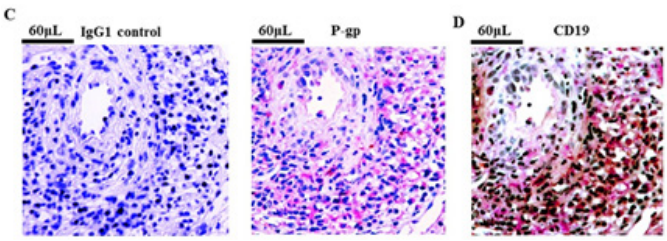

Figure 1C-D: True renal lupus vasculitis and P-glycoprotein expression on CD19+ cells. C-D: Immunohistochemical staining of serial 5-μm thick sections from the same specimens showed that the majority of these inflammatory cells were P-gp- (C) and CD19-positive cells (D). Immunostaining for P-gp (P-gp) on lymphocytes using JSB-1 anti-P-gp mAb (a murine mAb, dilution, 1:20; MONOSAN, Uden, The Netherland) or isotype-matched negative control antibody immunoglobulin G1 (IgG1 control; mouse IgG1, dilution, 1:10; DAKO, Glostrup, Denmark) or CD19+ cells (CD19) using anti-CD19 monoclonal antibody (mAb) with Vulcan Fast Red Chromogen Kit 2 (red color; Biocare Medical). Nuclear counterstaining with Meyer's hematoxylin.

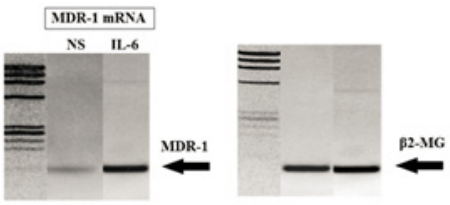

Figure 2: Up-regulation of transcription of multidrug resistance-1 in lymphocytes. Multidrug resistance -1 (MDR-1) mRNA expression was examined by RT-PCR using total RNA extracted from PBMCs incubated with 10 ng/ml of IL-6 or no stimulation (NS). The primer sequences were human β2-microglobulin (β2-MG) forward 5'-ACCCCCACTGAAAAAGATGA-3', reverse 5'-ATCTTCAAACCTCCATGATG-3'; human MDR-1 forward 5'-CCCATCATTGCAATAGCAGG-3', reverse 5'-GTTCAAACTTCTGCTCCTGA-3'. Amplified products were electrophoresed with Marker 4 (Nippon Gene, Tokyo) on 3% agarose gels.

Furthermore, IL-6 stimulates B cell differentiation into immunoglobulin-secreting cells. Serum levels of IL-6 are usually high in patients with SLE, and the levels often correlate with disease activity or with titers of autoantibodies. In addition, patients with active proliferative LN are found to have high urinary excretion rates of IL-6 [27]. The expression level of P-gp is significantly high on most peripheral CD19+ B cells activated by various stimuli in SLE patients, whereas the level is marginal in normal subjects (Figure 3A).

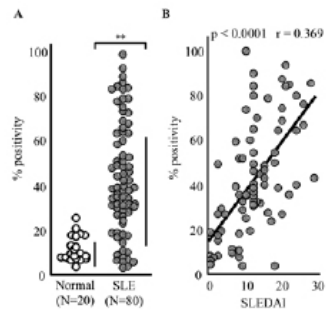

Figure 3A&B: Expression of P-glycoprotein on peripheral CD19+ cells from patients with systemic lupus erythematosus (SLE), as determined by flow cytometry. A, P-glycoprotein (P-gp) expression on peripheral CD19+ cells from 20 normal volunteers (open circles) and 100 SLE patients (hatched circles). Data are mean±SD. p value was determined by non-paired t-test. B, P-gp expression on CD19+ cells correlated closely with disease activity, as estimated by the SLEDAI score.Pearson's correlation analysis was used to determine statistical significance. n= 100.

In SLE patients, expression of P-gp on B cells correlates significantly with disease activity estimated by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score and results in the development of P-gp-mediated multidrug resistance against corticosteroids and failure to control disease activity (Figure 3B) [8, 9].

Experimental and clinical evidence suggests the involvement of P-gp in the migration of various inflammatory and cancer cells [28-32]. For example, high expression of P-gp is associated with metastasis and poor prognosis in patients with breast cancer [29]. Furthermore, P-gp-specific inhibitors reduce in vitro migration of breast cancer cells [30].

P-gp expression on leukemia cells correlates with disease aggressiveness and enhanced invasiveness [31, 32]. In highly active rheumatoid arthritis (RA), massive infiltration of P-gp+CXCR4+CD19+ B cells is noted in CXCL12-expressing inflammatory lesions of RA synovitis and RA-associated interstitial pneumonitis and expansion of these cells in peripheral blood reflects serious organ involvement [33].

On the other hand, the plasmablasts of the plasma-cell compartment contribute to pathogenesis of SLE through the expression of CXCR4 and CD19 [34]. Plasmablasts expansion has been described in patients with LN and such increase occurs just before relapse after B cell-depleting treatments [35, 36]. Actually, SLE patients with highly active disease state (ISN/RPS class III LN) shows expansion of peripheral CXCR4+CD19+ B cells (Figure 3C, Before&After).

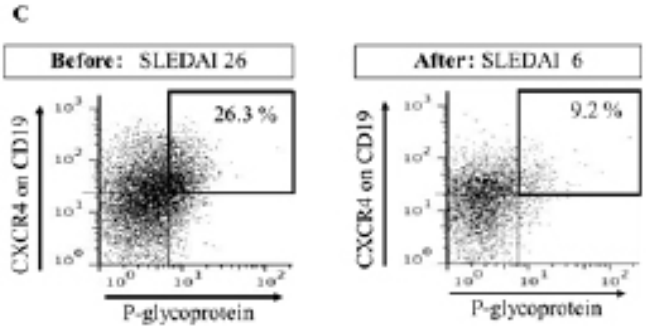

Figure 3C: Expression of P-glycoprotein on peripheral CD19+ cells from patients with systemic lupus erythematosus (SLE), as determined by flow cytometry.
C. Treatment with high-dose intravenous cyclophosphamide (IVCY) eliminates P-glycoprotein (P-gp)-highly-expressing B cells co-expressing CXCR4 in a representative SLE patient with ISN/RPS class III LN resulting in improvement of clinical disease activity estimated by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Flow cytometric analysis showed P-gp+CXCR4+ CD19+ cells just at the addition (Before) of intensive immunosuppressive treatment including biweekly IVCY at 6 weeks after (After) commencement of the treatment. Percentages represent the proportion of P-gp+CXCR4+CD19+ cells. The specific antibodies used for staining and flow cytometric analysis included PE-conjugated CXCR4 mAb (BD Biosciences Pharmingen)."

In SLE patients, memory B-cells often switch to the CD27-IgD- phenotype, which are activated switched-memory B cells that lost CD27 expression [37-39]. CD27-IgD- memory B cells are associated with auto-antibody titers, increased disease activity and renal disease in lupus patients [38-39].

Furthermore, IgD-CD27- memory B cells are reported to increase just before relapse in LN [35, 36]. In healthy donors, P-gp is exclusively present on mature CD27- naive B cells [40]. Patients with active LN harboring CD27-IgD-B cells show P-gp expression on CD27-B cells, including CD27-IgD-B cells (Figure 3D, Before&After).

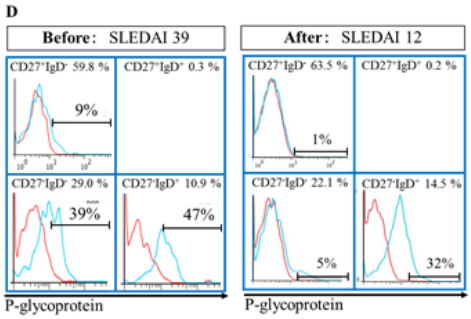

Figure 3D: Expression of P-glycoprotein on peripheral CD19+ cells from patients with systemic lupus erythematosus (SLE), as determined by flow cytometry. D. Treatment with IVCY eliminates P-gp-highly-expressing IgD-CD27-CD19+ B cells in a representative SLE patient with ISN/RPS class II LN, resulting in improvement of clinical disease activity estimated by SLEDAI. Values shown at the top of each compartment are percentages of CD19+B cell subpopulations based on CD27/IgD classification. Flow cytometric analysis showed P-gp expression on each B cell subpopulations (blue lines) just at the time of addition (Before) of intensive immunosuppressive treatment including biweekly IVCY and at 8 weeks after (After) commencement of the treatment. Data represent the percentages of P-gp-positively stained B cell subpopulations. Red: isotype-control FITC-conjugated anti-mouse IgG Ab. CD27+IgD+CD19+ B cells did not meet the number that P-gp expression analysis was possible. The specific antibodies used for staining and flow cytometric analysis included APC-conjugated CD27 mAb, and PE-conjugated IgD mAb (BD Biosciences Pharmingen).

While further studies are needed to fully understand the pathogenesis of TRLV, it is currently clear that activated plasmablasts and CD27-IgD- memory B cells, which often express P-gp, seem to be the main orchestrators of TRLV through their direct infiltration into the renal small vessels and through the production of autoantibodies.

Consequently, targeting these B cells seems a logical approach to control disease activity in refractory TRLV (Figure 4).

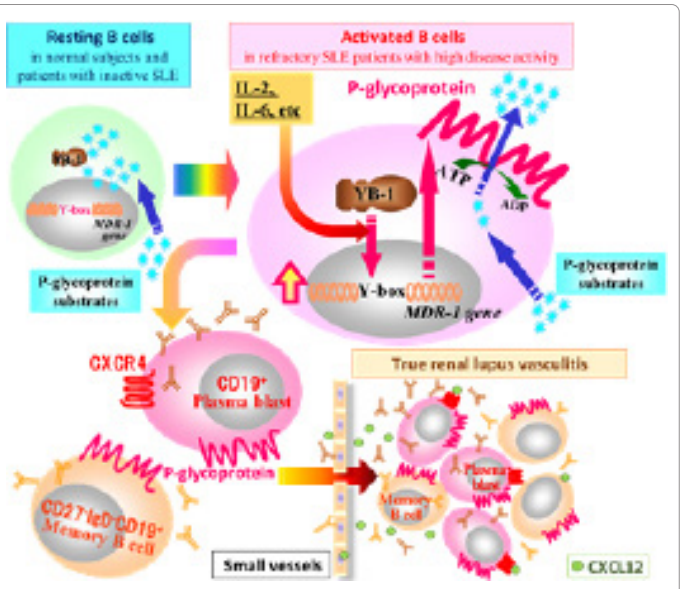

Figure 4: Schematic diagram of the relevance of P-glycoprotein (P-gp) expressing-activated B cells to the pathogenesis and resistance to treatment in True renal lupus vasculitis (TRLV). YB-1 is located in the cytoplasm of lymphocytes and P-gp is only marginally expressed on lymphocytes of normal subjects and patients with inactive SLE. In patients with highly active SLE, various stimuli induce P-glycoprotein expression on B cells, which leads to active efflux of drugs from B cells, resulting in drug-unresponsiveness and failure to control disease activity. Activated P-gp+CXCR4+ plasmablasts and P-gp+CD27-IgD- memory B cells might be the main orchestrators of TRLV through their direct infiltration into the renal small vessels and through production of autoantibodies.

OVERCOMING REFRACTORY TRLV WITH ACTIVATED-B CELL-TARGETING THERAPIES

Previous studies indicate that TRLV is always associated with lupus glomerulonephritis. In patients with LN classified as ISN/RPS class I/II, corticosteroid therapy is recommended, whereas the combination of high-dose corticosteroids and immunosuppressive therapies is recommended in class III/V [1]. The main effect of corticosteroids is on memory B cells and plasmablasts. Steroid therapy reduces peripheral memory B cells in children with steroid responsive nephrotic syndrome [41] while long-term corticosteroid therapy reduces peripheral plasmablasts in patients with autoimmune hemolytic anemia [42]. However, based on the pathogenic roles of P-gp-overexpressing memory B cells and plasmablasts, TRLV is fundamentally a multidrug-resistant condition. Therefore, failure to control renal manifestations of TRLV may occur with both the use of oral corticosteroid monotherapy and the use of combination therapy of corticosteroids plus other drugs of P-gp substrates (Table 1).

Table 1: Relation of P-glycoprotein with disease modifying antirheumatic drugs and immunosuppressants.

Drug	Pharmacological substrates of P-glycoprotein
Corticosteroids	YES
Cyclosporine	YES
Tacrolimus	YES
Methotrexate	NO
Mycophenolate mofetil	NO
Cyclophosphamide	NO
Leflunomide	NO
Azatioprine	NO
Hydroxycloroquine	YES
Salphasalazine	YES
Colchicines	YES

Conventional immunosuppressants, such as cyclophosphamide, mycophenolate and azathioprine, can result in sufficient inhibition of generation of plasmablasts. Previous case reports of TRLV showed favorable outcome with induction of remission by intravenous cyclophosphamide pulse therapy combined with high-dose corticosteroid before maintenance with mycophenolate or azathioprine [12-14]. Our group compared the therapeutic outcome of corticosteroid monotherapy versus combination therapy. We analyzed P-gp expression on peripheral B cells in 10 refractory SLE patients with high disease activity and SLEDAI score of more than 12 points, despite being treated with more than 0.5 mg/kg/day of prednisolone.

Marked P-gp overexpression on peripheral B cells was noted in all 10 patients. However, the addition of intravenous infusion of cyclophosphamide in 6 of the 10 patients and the use of 1 g of methyl-prednisolone pulse therapy in 2 of the 10 patients resulted in successful control of disease activity, as demonstrated by marked reduction in P-gp on B cells in all 10 patients [8]. Specifically, the reduction in peripheral P-gp+CD27-IgD-CD19+ B cells or P-gp+CXCR4+CD19+ B cells after the addition of immunosuppressive therapy to existing corticosteroid therapy is followed by clear improvement in clinical manifestations (Figure 3C and D, After).

On the other hand, the effect of conventional immunosuppressants is dependent on the rate of proliferation of these cells. Therefore, nonproliferating memory B cells are reported to be more resistant to conventional immunosuppressive therapy [43, 44].

Treatment with tocilizumab, which blocks IL-6, decreases peripheral plasma cell compartments and significantly diminishes anti-dsDNA antibody levels [45]. In patients with SLE, blockade of the IL-6 receptor reduces lymphocyte activation and restores B cell and T cell homoeostasis by either blocking the differentiation and/or trafficking and leads to normalization of the abnormal B and T cell subsets seen at baseline [46]. Moreover, blockade of IL-6 as the P-gp inducer may also reduce the expression of P-gp on activated B cells.

Rituximab, an anti-CD20 monoclonal antibody, largely depletes peripheral B cells, including memory B cells, and results in impairment of plasmablastogenesis. Clinical studies suggest that rituximab is a promising therapeutic agent against AASV and LN. Rituximab is reported to have induced remission in a patient with refractory TRLV [14] and several patients with relapsing LN

refractory to standard therapies [47]. Analysis of SLE patients found to respond well to long-term treatment with rituximab showed that rituximab induced rapid disappearance of IgD-CD27- memory B cells in the peripheral blood (within 28 days), followed by a much slower but definite complete disappearance of peripheral plasmablasts (within six months) [35]. Furthermore, in patients with ISN/RPS Class III/IV/V LN, a cocktail of rituximab, mycophenolate mofetil and methyl prednisolone pulse infusion (two 500 mg doses on days 1 and 15) was reported to achieve 90% complete or partial remission without oral corticosteroids [48].

CONCLUSION

Activated B cells, especially P-gp+CD27-IgD- memory B cells and P-gp+CXCR4+CD19+ plasmablasts, seem to play important roles in the pathogenesis of TRLV, resulting in the development of treatment resistance and poor renal outcome. P-gp overexpressing-activated B cells may expand, enter the peripheral circulation and home into inflammatory lesions. While there is urgent need for further clinical trials to establish the therapeutic and clinical effects of B cell-targeting therapies in the treatment of TRLV, it is important to introduce existing B cell-targeting therapies soon after diagnosis of TRLV in order to improve renal function and overall prognosis. Examination of the subsets of peripheral P-gp+ B cells in TRLV patients could help in the selection of treatment strategy including reinforcement of P-gp or B cell-targeted therapy.

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DECLARATION

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