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Brief Communication

Relapsing Evans syndrome and systemic lupus erythematosus with antiphospholipid syndrome treated with Bortezomib in combination with plasma exchange

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ABSTRACT

Relapsing Evans syndrome (ES) and systemic lupus erythematosus (SLE) with secondary antiphospholipid syndrome (APS) is very rare association. Coexistence of these syndromes is potentially fatal and require high-dose combined immunosuppressive therapy. We describe a case of successful use of Bortezomib and plasma exchange in a patient with ES and APS refractory to standard therapy. Thirty-two-year-old male who presented episodes of relapsing hemolytic anemia, pancytopenia and multiple thrombosis with positive direct and indirect antiglobulin test result, lupus anticoagulant and medium titer of anti-beta-2-glycoprotein 1 and anti-cardiolipin antibodies was diagnosed with ES and SLE with secondary APS. High-dose therapy by steroids and Cyclosporin A were started with temporary improvement. There was also no stable improvement with Rituximab and Cyclophosphamide. Bortezomib in combination with cyclosporine A and plasma exchange was introduced. He had stable improvement in hematological parameters with no evidence of relapse of hemolytic crisis or thrombosis during a follow-up for 1 year.

1. Introduction

The presence of autoimmune hemolytic anemia (AIHA) in conjunction with immune-mediated thrombocytopenia characterizes Evans syndrome (ES). Although anemia and thrombocytopenia are common features of systemic lupus erythematosus (SLE), ES is a rare manifestation in systemic lupus SLE. Coexistence of antiphospholipid syndrome (APS) with AIHA and APS with ES displays a frequency of 4% and 10%, respectively [1,2]. As the first-line therapy for ES glucocorticosteroids (GC) and intravenous immunoglobulin (IVIG) are typically used. The second-line therapy includes immunosuppressive agents, the monoclonal antibody Rituximab, or chemotherapy (vincristine). In 2008 Rückert et al. reported a case of APS with ES successfully treated with a combination of rituximab and cyclophosphamide [3]. Here, we present a clinical history of refractory ES and SLE with APS successfully treated with Bortezomib (BTZ) that led to steady clinical and serological improvement for both syndromes.

2. Clinical case

A 32-year-old man with history of recurrent deep vein thrombosis was admitted to our institution with fever, dyspnea and episode of nasal bleeding, life-threatening hemolytic anemia (Hb = 68 g/L) and pancytopenia (RBC = 2,29 ∗ 109/L, WBC = 1,75 ∗ 10^9/L, PP = 4800/μL). Laboratory signs of hemolysis were found (lactate dehydrogenase (LDH) was 655 U/L, reticulocytes were 5%, direct and indirect antiglobulin test were positive). The enzyme-linked immunosorbent assay (ELISA kits, Orgentec Diagnostica, Germany) was used to detect the level of antibodies several times during the disease course. Titers of antibodies to beta-2-glycoprotein 1 IgG (51 U/mL; cut-off 8 U/mL), beta-2-glycoprotein Ig M (11 U/mL; cut off 8 U/mL), anticardiolipin antibodies IgG (45 U/mL, cut-off 10 U/mL), anti-dsDNA antibodies

Abbreviations: AIHA, autoimmune hemolytic anemia; APS, antiphospholipid syndrome; BTZ, Bortezomib; ES, Evans syndrome; GC, glucocorticosteroids; Hb, hemoglobin; INR, international normalized ratio; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; SLE, systemic lupus erythematosus

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(2,45 IU/mL, cut-off 20 IU/mL) were displayed. Lupus anticoagulant (LAC) ratio was 1,63 (dRVVT tests according ISTH guidelines, normal range 0,80-1,20, Roche Diagnostics, Switzerland). Antinuclear antibodies were measured by indirect immunofluorescence assay (EUROPLUS ANA Mosaic 20A, Euroimmun, Germany) was negative (titer < 1/160). We determine low level of complement components C3, C4 by turbidimetry (C3 level 0,23 g/L, Reference range 0,75–1,65; C4 level 0,05 g/L, Reference range 0,13–0,54 g/L, Biosystems S.A., Barcelona (Spain)).

Physical and instrumental examination revealed livedo reticularis, oral mucosal ulceration, leg ulcers, and serositis (pleuritis and pericarditis). During hospitalization high activity of SLE was noted (SLEDAI 11, activity 3). He was treated with indirect oral anticoagulant (warfarin, 2.5 mg per day with a target of the international normalized ratio (INR) between 3.0 and 4.0) in consequence of thrombosis of Vena Cava Inferior and deep veins of the left lower limb in 2010. We prescribed Glucocorticoids (GC) (60 mg per day) and Cyclosporin A (300 mg per day) with gradual tapering of GC dose.

Recurrences of hemolysis re-appeared during GC tapering below 30 mg/daily. At the same time in spite of the full dose anticoagulant medication the patient developed splenic infarction, left iliofemoral thrombosis, pulmonary embolism, and thrombosis of the superior vena cava. Laboratory studies demonstrated thrombocytopenia, anemia, elevated lactate dehydrogenase (LDH), acanthocytes on blood smear, positive direct and indirect antiglobulin test (anti-IgG, anti-C3 antibodies), normal activity of ADAMTS13, normal D-dimer level. Malignancy, homocysteinemia, antithrombin III deficiency, protein C or S deficiency, factor V Leiden mutation, prothrombin A20210 mutation were excluded. We initiated second-line therapy with Rituximab (2000 mg IV), three pulses of GC 1000 mg, followed by 60 mg P.O. GC, and cyclosporine A 150 mg P.O. per day.

After 6 months improvement, the patient complained of low-grade fever, weakness, loss of appetite, arthralgia, and recurrence of oral mucosal ulceration and hemolytic anemia. The relapse was controlled with Rituximab (2000 mg IV) and Cyclophosphamide (500 mg IV). The attempts to reduce the dose of GC below 17.5 mg/daily provoked another relapse of severe hemolysis. Considering already published papers on the effectiveness of proteasome inhibitors in AIHA we decided to start the therapy with BTZ 1.3 mg/m^2/dose IV/SC twice weekly for 2 weeks followed by a 10-day wash-out period [4,5]. Before 6 cycles of BTZ therapy two rounds of plasma exchange therapy carried out. Dramatic clinical and laboratory improvement was noted in 6 weeks and was associated with suppression of hemolysis with negative Coombs serology, decrease of LDG, an increase hemoglobin level, improvement of leukopenia and thrombocytopenia, livedo reticularis regression and an increase of C3, C4 levels (Fig. 1). Currently the patient has been treated with prednisolone 10 mg per day, Cyclosporin A 200 mg, BTZ (1.3 mg/m^2/dose every 3 weeks), Plaquenil (200 mg twice a day) with no evidence of relapse of hemolytic crisis or thrombosis during a follow-up for 1 year.

3. Discussion

We present a case report of a stable remission of relapsing ES and SLE- APS treated with Bortezomib and plasma exchange after non responsiveness to a combination therapy with medium/high dose GC, Cyclosporine A, Rituximab and Cyclophosphamide.

Considering the presence of oral mucosal ulceration, no-erosive arthritis, serositis (pleuritis and pericarditis), hematologic syndrome (leucopenia, thrombocytopenia, hemolytic anemia), immunologic syndrome (aPL, low level of complement), CNS disorder (episode of seizures) the diagnosis SLE was verified according ACR criteria (6 of 11 criteria) and SLICC. It this case it was difficult to differentiate seronegative SLE with secondary APS and primary APS with multiple non-criteria appearance but serositis and articular syndrome are more characteristic for SLE.

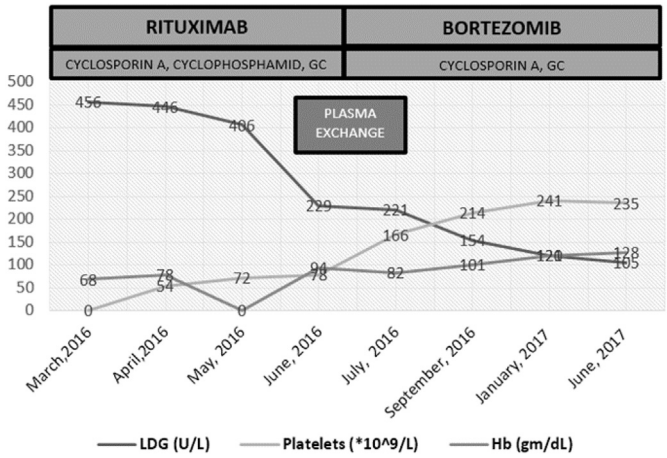

Fig. 1. Timecourse of Lactate Dehydrogenase level, platelets amount, hemoglobin level, GC – glucorticoids, LDG – lactat dehydrohenase level, Hb – hemoglobin level.

Both APS and AIHA are mediated by pathogenic autoantibodies produced by an aberrant response of the immune system against autoantigens [6,7] The mechanism of action of proteasome inhibitors (PIs) is based on the inhibition of nuclear transcription factors, on the regulation of proinflammatory cytokine release and on apoptosis induction. Plasma cells are extremely sensitive to PIs. Besides being identified in the treatment of B cell and plasma cell-related hematological malignancies, BTZ have been also used in some autoimmune disease. There are three clinical trials of BTZ: refractory cold agglutinin disease, IgA nephropathy, proliferative lupus nephritis. [8]

A successful use of BTZ in refractory AIHA was also reported [4,5]. Based on recent published series, patients suffering from systemic lupus erythematosus who received intravenous BTZ (1.3 mg/m2) displayed increase in serum complement C3 levels and a significant reduction of anti-dsDNA, anti-Sm, anti-RNP/Sm and anti-Ro/SSA autoantibodies [9,10]. Currently there are no data about the use of BTZ for treatment of ES or APS.

The reported clinical case was not responsive to GC and to rituximab alone or in combination with Cyclophosphamide and Cyclosporine. We describe for the first time a successful treatment of relapsing ES and SLE with APS with a long follow-up (1 year) persistently free of clinical recurrences. The major limitation of our clinical case is the fact that we also used other strong immunosuppressants in the treatment and we cannot extrapolate the efficacy of BTZ monotherapy. However, BTZ treatment allowed to reduce the dose of GC to 10 mg/day and the patient went into clinical remission with absence of other hematological or thrombotic complications.

4. Conclusion

Unfortunately, we did not observe stable decrease of anti-beta-2-glycoprotein 1 and anti-cardiolipin during BTZ therapy. Still is not clear the pharmacological mechanism of action of PIs in these autoantibody-mediated disorders, since BTZ inhibited the production of the anti-erythrocyte antibodies but this was not the case for antiphospholipid antibodies. A combination of plasma exchange followed by BTZ, low GC doses and cyclosporine A may be a rescue therapy in resistant cases of SLE with APS and ES.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

[1] R.A. Asherson, M.A. Khamashta, J. Ordi-Ros, R.H. Derksen, S.J. Machin, J. Barquinero, H.H. Outt, E.N. Harris, M. Vilardell-Torres, G.R. Hughes, The "primary" antiphospholipid syndrome: major clinical and serological features, Medicine (Baltimore) 68 (1989) 366–374 http://www.ncbi.nlm.nih.gov/pubmed/2509856.

[2] C.G. Mackworth-Young, S. Loizou, M.J. Walport, Primary antiphospholipid syndrome: features of patients with raised anticardiolipin antibodies and no other disorder, Ann. Rheum. Dis. 48 (1989) 362–367, https://doi.org/10.1136/ard.48.5.362.

[3] A. Ruckert, H. Glimm, M. Lubbert, C. Grullich, Successful treatment of life-threatening Evans syndrome due to antiphospholipid antibody syndrome by rituximab-based regimen: a case with long-term follow-up, Lupus 17 (2008) 757–760, https://doi.org/10.1177/0961203307087876.

[4] K.R. Carson, L.G. Beckwith, J. Mehta, Successful treatment of IgM-mediated autoimmune hemolytic anemia with bortezomib, Blood 115 (2010) 915, https://doi.org/10.1182/blood-2009-09-242917.

[5] Y. Wang, W. Zhou, Z. Zhang, Successful treatment of warm-type haemolytic anaemia with bortezomib in a rituximab-failed systemic lupus erythematosus patient, Rheumatology (Oxford) 54 (2015) 194–195, https://doi.org/10.1093/rheumatology/keu393.

[6] E.M. Meulenbroek, D. Wouters, S.S. Zeerleder, Lyse or not to lyse: clinical significance of red blood cell autoantibodies, Blood Rev. 29 (2015) 369–376, https://doi.org/10.1016/j.blre.2015.05.001.

[7] P.L. Meroni, M.O. Borghi, E. Raschi, F. Tedesco, Pathogenesis of antiphospholipid syndrome: understanding the antibodies, Nat. Rev. Rheumatol. 7 (2011) 330–339, https://doi.org/10.1038/nrrheum.2011.52.

[8] S.C. Yeo, A. Liew, J. Barratt, Emerging therapies in immunoglobulin A nephropathy, Nephrology 20 (2015) 788–800, https://doi.org/10.1111/nep.12527.

[9] T. Alexander, R. Sarfert, J. Klotsche, A.A. Kühl, A. Rubbert-Roth, H.-M. Lorenz, J. Rech, B.F. Hoyer, Q. Cheng, A. Waka, A. Taddeo, M. Wiesener, G. Schett, G.-R. Burmester, A. Radbruch, F. Hiepe, R.E. Voll, The proteasome inhibitior bortezomib depletes plasma cells and ameliorates clinical manifestations of refractory systemic lupus erythematosus, Ann. Rheum. Dis. 74 (2015) 1474–1478, https://doi.org/10.1136/annrheumdis-2014-206016.

[10] H. Zhang, Z. Liu, L. Huang, J. Hou, M. Zhou, X. Huang, W. Hu, Z. Liu, The short-term efficacy of bortezomib combined with glucocorticoids for the treatment of refractory lupus nephritis, Lupus 096120331668670 (2017), https://doi.org/10.1177/0961203316686703.