CASE REPORT

Effective treatment of antiphospholipid syndrome with plasmapheresis and rituximab

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Abstract
With the exception of the catastrophic antiphospholipid syndrome (APS), the management of patients with APS has been largely supportive aiming at avoiding a recurrent thrombotic event; it is noteworthy that data concerning therapy targeting the triggering factor (the antiphopsholipid antibodies) are scarce. We report a case of APS manifested as recurrent fetal losses, ischemic stroke and renal dysfunction with concomitant nephrotic syndrome successfully treated with the combination of plasmapheresis and anti-CD20 antibody. Hippokratia 2010; 14 (3): 215-216

Key words: antiphospholipid syndrome, pregnancy, plasmapheresis

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The antiphospholipid syndrome (APS) is characterized by a constellation of clinical features including venous and arterial thrombosis, recurrent fetal losses, and thrombocytopenia attributed to the presence of antibodies directed against either phospholipids or plasma proteins bound to anionic phospholipids[1]. Either primary (when it occurs alone), or secondary (in association with systemic lupus erythematosus - SLE, other rheumatic diseases, certain infections and drugs), the treatment of APS is largely supportive. Based on the use of heparin, warfarin, antiplatelet agents and hydroxychloroquine, current treatment aims at avoiding recurrent thrombotic events without targeting the antibodies that are responsible for the pathogenesis of the syndrome.

We selected to target our treatment to the causative agent (the antiphospholipid antibodies) and therefore we used a combination of plasmapheresis and rituximab aiming at reducing the serum antibody levels via the former and inhibiting their production via the latter.

Case

A 30 year old pregnant (15/40) lady was referred to the renal unit of our hospital on 5/10/2004 because of nephrotic range proteinuria (5.2g/24h) and renal dysfunction (Scr=1.5 mg/dl, eGFR (MDRD) =51,55 ml/min). She had 3 previous pregnancies that resulted in intrauterine deaths after the 10th week of gestation, a history of ischemic stroke in the right parietal lobe (1 year before presentation) and a history of Raynaud's phenomenon. Despite this impressive history a thrombophilia screen was never performed and the patient was not on any medication. On examination, her blood pressure was 130/85, she had clubbing and livedo reticularis. A full thrombophilia screen revealed anticardiolipin antibodies (ACA-IgG:84,0 GPLU/ml and IgM:14,5 MPLU/ml, normal range <15,0 and <12,6 respectively). She was also found to have antinuclear antibodies in a low titer 1/160. All other lupus serology was negative. She was started on low molecular weight heparin and was followed weekly in the outpatient clinic. Two weeks later she had another miscarriage and delivery revealed a dead embryo.

One month later and while proteinuria persisted, a renal biopsy showed focal segmental glomerulosclerosis and one arteriole with fibrinoid necrosis and an intraluminal thrombus. A detailed thrombophilia screening and lupus serology were repeated reconfirming the abovementioned results. A diagnosis of primary antiphospholipid syndrome was made and she was started on plasmapheresis. After an initial course of 6 alternate day plasmapheresis sessions she was maintained on biweekly treatments for 2 weeks, then once weekly for a month and once monthly thereafter. The ACA titer came down to IgG: 26 GPLU/ml and IgM: 1 MPLU/ml respectively and the proteinuria decreased to <500 mg/day. Consequently, the patient received the monoclonal antiCD20 antibody rituximab of which she had a course of 375mg/m^2 in 4 weekly doses. The patient was followed monthly in the renal clinic thereafter. She was receiving aspirin (100 mg o.d), irbesartan (150 mg o.d) and amlodipine 10 (mg o.d) for her hypertension and for the control of Raynaud's manifestations. The ACA titer remained low for the next 12 months, renal function was stable, proteinuria remained <500 mg and the patient was symptom free. A year after diagnosis, the patient was hospitalized for an episode of generalized seizures accompanied by transient loss of consciousness and post ictus lethargy. The ACA titre was not increased, the magnetic resonance angiography was normal and a diagnosis of epilepsy secondary to the old infarct was established. The patient was started on levetiracetam (1g b.d) and was discharged a few days

later. Three months after this episode, the ACA titre began to rise (IgG: 21 GPLU/ml and IgM: 14MLPU/ml) while the patient was symptom free. Plasmapheresis was intensified and the patient received a second course of anti-CD20 (2 doses of 1g each, dosing interval 15 days). The ACA titre fell rapidly (over 10 days) to normal levels and remained low since then. The patient has remained symptom free, with stable renal function and proteinuria 600 mg/day since then (1 year follow-up since the second rituximab infusion), and is attending the outpatient renal clinic monthly.

Discussion

In this case report, a combined treatment with plasmapheresis and anti-CD20 antibody infusion resulted in successful control of a severe form of the APS. Plasmapheresis with or without IVIG have been used in the past in cases of catastrophic APS and when features of microangiopathy (eg, thrombocytopenia, microangiopathic hemolytic anemia) are present[2-4]. In these cases high dose corticosteroids are routinely used as well. Although our case did not fulfil all the criteria for the diagnosis of catastrophic APS, she did have serious thrombotic episodes involving three organs (brain, kidney, placenta) and we had lab confirmation of the presence of antiphospholipid antibodies when she came to our department. The fact that the thrombotic episodes were intermittent, with periods free of thrombosis, even without treatment, is consistent with a current theory on the pathogenesis of APS which maintains that a "second hit" is required for the development of the full blown syndrome[5]. Our patient had multiple factors predisposing to this second hit (pregnancy, nephrotic syndrome, and hypertension) but after each event the syndrome seemed to settle down on its own.

Therapy for the non-catastrophic APS is largely the same regardless of whether the disorder is classified as primary APS or as being secondary to SLE. Current therapies that include unfractionated and low molecular weight heparin, warfarin, antiplatelet agents and hydroxychloroquine do not target the disease specific antibodies but aim at reducing recurrent thromboembolic events. A review of the literature showed that only 12 case reports on the use of rituximab in patients with primary, secondary and catastrophic APS have been published[6]. We used a combined "aggressive" approach with plasmapheresis (to remove the circulating antiphospholipid antibodies from the serum) and rituximab (to reduce the production of these antibodies) aiming both at rapidly decreasing the antibody load that was responsible for the clinical manifestations of the disease and preserving this decrease in the long term thus minimizing the risk for recurrence. We believe that our approach was successful since we managed to control a severe form of the APS with diverse manifestations: no clinical recurrence has occurred so far, renal function has remained stable and proteinuria has shown a sustained remission.

However, this is a case report and definite conclusions can not be drawn concerning the effectiveness of plasmapheresis and rituximab for the long term control of the APS. Moreover, we were not able to monitor B cell count following rituximab administration to assess the effectiveness of the dosing regimen on target cells (B cells).

Conclusion

We describe a successful approach for the treatment of severe APS, using the combination of plasmapheresis and anti-CD20 antibody. We believe that this approach might prove to be beneficial for patients with APS.

No conflict of interest is declared

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