MICROANGIOPATHY IN SLE: A DIAGNOSTIC AND THERAPEUTIC CHALLENGE

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Thrombotic microangiopathy is a syndrome that comprises several disorders characterised by localised or diffuse microvascular thrombosis.^{1 2} These include the catastrophic antiphospholipid syndrome (CAPS),³ thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), disseminated intravascular coagulation (DIC) in the context of systemic infections or malignancies, hypertension-related, pregnancy-related and drug-related microangiopathic syndromes, and heparin-induced thrombocytopenia.⁴ Some of these clinical scenarios such as severe preeclampsia and HELLP syndrome may be suspected given the appropriate clinical context such as pregnancy. In other cases, the most important point is to perform a systematic and complete clinical history and physical examination looking for previous thrombosis or pregnancy morbidity, uncontrolled hypertension, bloody diarrhoea, and exposure to heparin or some concrete drugs such as ticlopidine, clopidogrel, chemotherapy agents, and alendronate that have been identified as probable cause of thrombotic microangiopathy. In addition, unexplained weight loss, gradual onset of symptoms, hepatomegaly or splenomegaly, or palpable lymphadenopathies may indicate the existence of malignancy triggering the thrombotic microangiopathy. High-grade fever accompanying chills may be the signs of systemic infection in the form of severe sepsis. A history of acute gastroenteritis with bloody diarrhea caused by verocytotoxin (Shiga-like toxin)-producing *Escherichia coli* but also *Shigella dysenteriae* type I and *Citrobacter freundii* might indicate HUS. In cases of severe hypertension, funduscopic exam is mandatory to rule out the evidence of exudates and papilla oedema pointing to a malignant hypertension.

However, differential diagnosis is not so easy in the real-world setting. On the one hand, the clinical picture may be very similar between different diseases.⁴ Kidney and neurologic involvement may be present in CAPS but also in malignant hypertension, severe sepsis, and TTP/HUS. Conversely, physicians should remember that in most causes of thrombotic microangiopathy, other than CAPS, antiphospholipid antibodies (aPL) may also be present. The aPL have been reported in some patients with TTP/HUS, but usually at low titers. In this context, a decrease in ADAMTS13 activity of fewer than 5% points to TTP as the most probable diagnosis. Infections are capable of inducing aPL but normally at low titer and they are not persistent over time. With all these data, in front of a patient with thrombotic microangiopathy, a comprehensive diagnostic workup should be carried out.

Learning Objectives

- Explain the main challenges in the differential diagnosis of microangiopathy in SLE
- Describe the treatment options for microangiopathy in SLE
- Discuss new trends in research on new markers for microangiopathy in SLE

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Plenary II: Novel Therapeutic Developments in 2020

PLASMA-CELL DIRECTED THERAPIES

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Autoantibodies of various specificities play key roles in the pathogenesis of systemic lupus erythematosus (SLE). They are directly responsible for manifestations such as autoimmune thrombocytopenia, autoimmune haemolytic anaemia, antiphospholipid syndrome, neonatal lupus/congenital heart block and most cases of transversal myelitis. In addition, autoantibodies to dsDNA and nucleosomes may essentially contribute to lupus nephritis.

Antibodies are produced by plasma cells. Short-lived plasma cells die within a few days after their differentiation, whereas long-lived plasma cells can live as long as the organism does. Most importantly, long-lived plasma cells are resistant to most conventional treatments including high-dose prednisolone, cyclophosphamide and anti-CD20 antibodies, because plasma cells are mostly devoid of CD20. Hence, refractory SLE may often be caused by long-lived plasma cells secreting pathogenic antibodies. For these reasons plasma cells represent an attractive target for the treatment of SLE and other antibody-mediated diseases.

Meanwhile, there are several treatments available, at least in clinical trials, which eliminate plasma cells including the long-lived ones:

- a. High-dose cyclophosphamide combined with anti-thymocyte globulin (also containing antibodies against plasma cells) and subsequent autologous stem cell transplantation. This vigorous procedure has substantial treatment-related morbidity and lethality, but, it can also cause an ‘immunological reset’ leading to long-term drug-free remissions of SLE. Of course, stem-cell transplantation affects most cells of the immune system, not only plasma cells.¹
- b. Proteasome inhibitors: Due to their extremely high production of antibodies within the endoplasmic reticulum, plasma cells are highly sensitive towards proteasome inhibition, which blocks the degradation of misfolded proteins, thereby inducing endoplasmic reticulum stress and the terminal unfolded proteins’ response leading to apoptotic cell death.² Proteasome inhibitors affect predominantly plasma cells, however, they may target also other cells with a very high synthesis of secretory proteins. We demonstrated that the proteasome inhibitor bortezomib, which is approved for treatment of multiple myeloma, can efficiently deplete short- as well as long-lived plasma cells in mice and thereby ameliorates murine lupus nephritis.³ Moreover, in a case series the outcomes of 15 SLE patients were analysed, who