I

PROLOGUE

A case history

A 27 year old Asian woman presented at the outpatient clinic of the department of rheumatology with a sudden onset of butterfly exanthema, alopecia, fever, and swollen joints of the hands and wrists. Laboratory tests revealed a rapid rise in serum creatinine, leuco- and thrombocytopenia, low levels of complement C3 and C4, positive antinuclear antibodies (ANA) and anti–double-stranded DNA (anti-dsDNA) antibodies. Urinalysis showed an active sediment suggestive of glomerulonephritis. She was diagnosed with systemic lupus erythematosus (SLE). To determine the stage of renal involvement, a renal biopsy was performed, which showed a membranous glomerulopathy and a full house immunofluorescence pattern, compatible with lupus nephritis class V. Prednisone therapy was initiated, after which her renal function stabilized, as did the other clinical symptoms.

Two years later, a second renal biopsy was taken because of declining renal function and pronounced proteinuria. A rise in anti-dsDNA and low levels of C3 and C4 were detected. The renal biopsy confirmed a renal flare, showing a diffuse proliferative glomerulonephritis compatible with lupus nephritis class IV. An abdominal ultrasound obtained for nausea and stomach ache, unexpectedly revealed a renal vein thrombosis in the right kidney. In addition to prednisone, pulse cyclophosphamide was administered, and treatment with vitamin K antagonists as anticoagulant therapy was initiated. The patient's condition and renal function stabilized after 13 cyclophosphamide pulses. The renal vein thrombosis led her clinicians to evaluate antiphospholipid antibody titers. Both anticardiolipin IgG and IgM ELISAs and the lupus anticoagulant test were negative. Therefore, it was decided to terminate the anticoagulant therapy after two years.

During this time, she was referred to a gynecologist for preconceptional counseling, and to assess whether there were signs of premature ovarian failure induced by cyclophosphamide therapy. She had no wish to become pregnant at that moment, but was considering pregnancy in a few years. The gynecologist discussed the potential dangers and difficulties of pregnancy in combination

with renal disease and SLE. The effect of pregnancy on lupus was set out against the effect of lupus on pregnancy and the fetus. Pregnancy in an SLE patient entails a high risk of lupus-flare, a high risk of renal-flare, a higher risk of hypertensive pregnancy disorders such as preeclampsia and HELLP syndrome and a higher risk of thrombosis. Inversely, SLE affects pregnancy and the fetus by inducing a higher risk of miscarriage, intrauterine growth restriction, (iatrogenic) preterm birth and even fetal death. Especially the presence of antiphospholipid antibodies reduces the chance of an uncomplicated pregnancy. Finally, the gynecologist talked about genetics and the teratogenic effect of certain medications.

It appeared that she was using an oral contraceptive pill for heavy menstrual periods, but not for contraception per sé. Due to the renal vein thrombosis, it was advised to stop oral contraception to reduce the risk of further thrombotic complications, even though antiphospholipid antibodies were still undetectable. Furthermore, it was decided that aspirin and a daily prophylactic dose of low molecular weight heparin during pregnancy were indicated in case she would become pregnant.

Unfortunately, within a year after the visit to the outpatient clinic of the department of gynecology she developed menopausal symptoms of flushing and an irregular menstrual cycle. Subsequent analysis showed premature ovarian failure, most likely induced by cyclophophamide pulse therapy.

Despite pulse cyclophosphamide and prednisone therapy, the patient's renal function gradually continued to decline during the following years; her blood pressure slowly increased to a mean of 180/100, and proteinuria rose to a nephrotic range. A third renal biopsy specimen was obtained when she was 36. This time, in addition to lupus nephritis class IV, histological evidence of a thrombotic microangiopathy was found. Anticoagulant treatment was resumed. A thorough diagnostic work-up for underlying causes of thrombotic microangiopathy was performed, in which antiphospholipid antibodies were still negative, but serological complement levels C3 and C4 appeared to be extremely low. Further analysis revealed no evidence for HUS, TTP, or other conditions related to thrombotic microangiopathy apart from active SLE.

Shortly thereafter, she presented with upper body ataxia and progressive aphasia, indicators of cerebral involvement of SLE which is known as neuropsychiatric SLE. She was treated with a high dose of immunosuppression, 10 plasmapheresis sessions and hemodialysis, but despite this treatment, her GFR had now declined to 15 micromoles/liter. Prolonged hemodialysis was started at the age of 39. Her condition stabilized, though permanent neurological injury had developed for which she was admitted to a rehabilitation center.

Two years later, she suffered acute neurologic deterioration and respiratory distress. She was admitted to the intensive care unit, where hemolytic anaemia, deep thrombocytopenia, multiple purpura and an oliguric state pointed at a recurrence of the thrombotic microangiopathy. Despite additional plasmapheresis sessions and high doses of immunsuppression she died, most likely due to diffuse alveolar hemorrhage and bleeding in and around multiple organs caused by severe thrombocytopenia, active lupus nephritis and widespread microthrombotic injury.

At autopsy, the kidneys showed signs of extensive chronic damage, classified as lupus nephritis class IVc. Furthermore, multiple fibrin microthrombi were present in glomeruli. In the brain, diffuse chronic and global ischemia was found, accompanied by several vessels in the white matter with intraluminal thrombi. For research-purposes, her kidney biopsy specimens and available tissue samples from the cerebral cortex were stained for complement factor C4d, which revealed diffuse and intense complement depositions in all affected organs.

This patient appeared as a subject in two out of four research articles described in this thesis (Chapter 4 and 5). The striking observation of widespread thrombo-ischemic injury in combination with extensive complement deposition served as a basis for many ideas and research questions that will be addressed in the following chapters. Most importantly, this case history underlines that all patients tell a story and that all medical science begins and ends with stories like these.