Clinical insights from observations on ADAMTS13 deficiency in liver cirrhosis

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Ten years ago ADAMTS13 (A disintegrin and metallopro-
tease with thrombospondin 1-like repeats) exploded into
the awareness of haematologists when a severe deficiency
of ADAMTS13 was associated with thrombotic thrombo-
ypenic purpura (TTP) (1, 2). ADAMTS13 is an enzyme in normal
plasma required for proteolysis of von Willebrand factor (VWF)
following its secretion from endothelial cells; the absence of
ADAMTS13 in the circulation leads to abnormally large
multimers of VWF which may spontaneously bind to circulating
platelets and result in microvascular thrombosis. As may occur
with strikingly original observations that reveal clear pathogen-
etic mechanisms for a critical illness, it was initially assumed
that ADAMTS13 would tell the whole story of TTP: severe
ADAMTS13 deficiency would be both necessary and sufficient
to cause TTP, and documentation of severe ADAMTS13 defi-
ciency would be both sensitive and specific for identifying pa-
tients with TTP. However, as may also occur, more experience
and less selectivity of patients have resulted in a more realistic
understanding of the role of ADAMTS13.

The observations by Uemura et al. (3) in this issue of Throm-
bosis and Haemostasis are an excellent example of our expan-
sive knowledge about ADAMTS13. Initially severe
ADAMTS13 deficiency was considered to be an abnor-
mality specific for TTP (4). Subsequent studies reported that severe
ADAMTS13 deficiency may also occur in patients with sepsis
and disseminated intravascular coagulation (5, 6). Uemura et al.,
following their previous observation that ADAMTS13 is syn-
thesized in hepatic stellate cells (7), have now clearly docu-
mented that patients with severe liver disease may also have se-
vere ADAMTS13 deficiency (3). Their observation is convinc-
ingly demonstrated by multiple experiments. The severity of
ADAMTS13 deficiency was related to the severity of liver dis-
ease. ADAMTS13 activity also correlated with many clinical
and laboratory parameters that describe the severity of liver dis-
ease. Deficient ADAMTS13 activity was confirmed by docu-
mentation of parallel deficiencies of ADAMTS13 antigen and
also by the presence of abnormally large VWF multimers.

What is the clinical importance of these observations? Al-
though a deficiency of ADAMTS13 activity creates a prothrom-
botic state (8, 9), this may not be apparent because of the coagu-
lation factor deficiencies and thrombocytopenia that also occur
in liver disease. In the study of Uemura et al. (3), five patients
with end-stage liver disease had undetectable ADAMTS13 but
only one had the clinical syndrome of TTP. Could the four other
patients with undetectable ADAMTS13 but absence of clinical
features of TTP have an indolent prothrombotic state with risk
for future complications? The authors speculate that these four
patients may have had “subclinical” TTP. Could a deficiency of
ADAMTS13 synthesis and secretion by the liver have a more lo-
calized prothrombotic in the liver itself? The authors propose
that ADAMTS13 deficiency could contribute to the common oc-
currence of portal and hepatic vein thrombosis in patients with
advanced liver cirrhosis. These observations are important not
only for a better understanding of the systemic manifestations of
severe liver disease; they are also important to stimulate ques-
tions concerning the role of ADAMTS13 in other disorders.

To return to TTP, which was the beginning of the
ADAMTS13 story, these observations may suggest new per-
spectives about TTP. For example, we have thought that TTP oc-
curs in discrete episodes, and that patients are either critically ill
or in complete remission. However, could the intensity of TTP be
variable? Does “subclinical” TTP exist? Persistent absence of
ADAMTS13 activity following remission from TTP may in-
crease the risk for a recurrent acute episode (10), but examples of
chronic, smoldering TTP, as opposed to intermittent acute epi-
isodes, are not currently recognized. However, in the era before
effective treatment, patients were described who had chronic
TTP manifested by intermittent neurologic abnormalities and
purpura (11). With more careful long-term follow-up of patients
following their recovery from an acute episode, continuing,
subtle manifestations of TTP may become apparent.

We have also thought that TTP is a disorder characterized by
systemic microvascular thrombosis. However, could the anat-
omic manifestations of TTP in some patients be selective? Pre-
vious experience has suggested that microvascular thrombosis may occur less frequently in the liver and lungs than elsewhere (12). But rather than specific organs being spared, could there be clinical situations in which specific organs are targeted by TTP? Thrombotic microangiopathies caused by multiple etiologies may be localized to the kidney (13), but none of these disorders are currently known to be associated with severe ADAMTS13 deficiency. However, patients with congenital absence of ADAMTS13 may develop progressive renal failure in the absence of overt acute episodes of TTP (14, 15).

The observations of Uemura et al. (3), as with all original clinical observations, are important not only for the disease that was studied but also for stimulating questions and creative insights that can help to understand other disorders.

References