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A Case of Renal Thrombotic Thrombocytopenic Purpura

With Comments on Coagulation and Immunofluorescent Studies

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Thrombotic thrombocytopenic purpura may mimic the classic picture of acute glomerulonephritis with acute renal failure, but may not necessarily manifest changing sensory and motor neurological findings or purpura, fever and hemolytic anemia.

Since the diagnosis in this case was made antemortem, it presented an opportunity to study associated coagulation parameters and tissue immunofluorescence, the results of which are discussed.

Case summary: M.H.S., a 26-year-old white woman was admitted to St. Luke’s Hospital, Saginaw, Michigan, on August 8, 1965, because of swelling of the hands and feet which had been present for one week earlier. Aside from a 14-pound weight gain and easy fatigability during this period she was otherwise asymptomatic.

Physical examination showed a blood pressure of 130/80, pulse rate 82 and respirations of 16 per minute. There was pallor of the skin but no evidence of purpura, ecchymosis or petechiae. Small discrete nodes were palpable in the supraclavicular spaces and posterior cervical triangles. The heart was not enlarged, there were no murmurs heard, and the rhythm was regular. Lungs were clear; no abdominal organs were palpable.

The following laboratory studies were obtained from Saginaw: Hemoglobin 8.6 gm%, hematocrit 26%, red blood cell count 3.1 million per cmm, white blood count 11,300/cmm. Urinalysis showed specific gravity 1.009, albumin 2 to 4 plus, 6 to 8 fine granular casts, 7 to 8 WBC and 45 RBC per high powered field. At time of admission the BUN was 62 mg%, rising subsequently to 85 mg%. Serum

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electrolytes were normal. ASO titer was 12 units/ml and the indirect Coombs test was negative. Serum complement level was within normal limits. Serum cholesterol was 143 mg\%, and serum protein electrophoretic pattern was normal, with a total protein of 5.4 gm\%. Bone marrow smear showed no diagnostic abnormality. Cervical lymph node biopsy showed no abnormalities.

Needle biopsy of the kidney is illustrated in Figure 1 and will be discussed later.

During the first six days in St. Luke's Hospital, the BUN rose to 85 mg\%, and the CO\textsubscript{2} fell to 13 mEq/1. Rising serum potassium levels were verified by electrocardiographic peaking of T waves. The patient became acutely dyspneic on the seventh day, with tachycardia and fever of 102°F (38.9°C). Chest x-ray indicated either uremic pneumonitis, or pulmonary edema, or both. Treatment of hyperkalemia consisted of insulin, glucose and calcium gluconate given intravenously. Shortly thereafter cardiac arrest lasting two minutes was followed by successful resuscitation and restoration of sinus rhythm. Peritoneal dialysis was started with hourly exchanges over a 24-hour period, after which the patient was transferred to the Henry Ford Hospital.

On admission, August 16, 1965, she was alert and comfortable. Blood pressure was 150/100, pulse rate 140 per minute, with a normal sinus rhythm. Small

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Figure 1
Thrombus has partially or completely occluded the longitudinally sectioned arteriole as well as isolated segments of glomerular capillaries (arrow).
H & E x 300

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supraclavicular nodes were palpable. The only ecchymotic areas were those associated
with needle puncture sites. No petechiae were noted. Moist rales were present at
both lung bases, and a grade III systolic murmur was heard over the precordium.
Abdominal examination was negative. Mild pedal edema was noted. Reflexes were
active and equal, with no pathologic toe or finger signs. Cranial nerves were intact.

Laboratory work demonstrated a hemoglobin of 9.4 gm%, hematocrit 3290, white
count 25,250/cmm with 91% neutrophils, 8% lymphocytes, and 1% metamyelocytes.
Large platelet forms were noted and the red blood cell morphology showed marked
anisocytosis and poikilocytosis. BUN was 75 mg%, creatinine 11.2 mg%, uric
acid 14.5 mg%, serum sodium 145 mEq/1, potassium 6.6 mEq/1, chloride 96
mEq/1, and CO2 24.5 mEq/1. Calcium was 8.7 mg%, and inorganic phosphate
5.2 mg%. Reticulocyte count was 14.9% and platelet count 70,000/cmm.

The patient was oliguric with the urine showing 2 plus albumin, clumps of
leukocytes and 8 to 10 red cells per high powered field. LE preparations were
negative. Fibrinogen level was 610 mg%. Bone marrow aspiration gave a myeloid-
erythroid ratio of 5.5:1, with good cellularity and increased numbers of developing
neutrophils. A deficiency of megakaryocytes was noted.

Figure 2
Lumen and wall of a renal glomerulus (A) and small renal artery (B) showing fibrinoid material.
Masson trichrome stain A-1100 X
B- 450 X

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Hospital course: Peritoneal dialysis was continued and by the fourth day the BUN had fallen to 29 mg%. The patient remained alert and oriented with a urine output from 0 to 100 mls/24 hours throughout her hospitalization. A precordial friction rub appeared on the second day. On the third day, a repeat episode of cardiac arrest occurred, followed later by EKG evidence of ventricular tachycardia. Cardiac massage, assisted ventilation, intravenous sodium bicarbonate, and pronestyl converted the arrhythmia to sinus rhythm. The patient’s sinus rhythm was maintained for only a few hours, then arrest occurred some thirty times, each requiring direct current shock for conversion. Coma followed these episodes. Details of the histopathology, including cardiac manifestations, have been previously reported by Dr. T. N. James.¹

Death occurred on the eighth hospital day, 23 days after onset of the patient’s illness.

Discussion

Since 1925, when Moschocowitz² described the triad of purpura, hemolytic anemia and neurologic deficits, two additional symptoms — fever and renal disease — have been added to form a pentad of manifestations of thrombotic thrombocytopenic purpura (TTP). The literature is replete with descriptions of case histories and pathologic findings, yet the etiology of this disease and the exact nature of the hyaline thrombi material is still obscure. Our comments will be confined mainly to the renal involvement in TTP with presentation and interpretation of coagulation studies in this patient.

Amorosi and Ultmann³ reviewed the literature and described renal features of thrombotic thrombocytopenic purpura manifested by azotemia, proteinuria, pyuria, casts and evidence of hyaline occlusions in the capillaries and arterioles. Proliferative nephritis has also been described.

More recently, acute anuric irreversible renal failure with TTP has been discussed by Dunea, et al.⁴ Their patients, although adults, had features resembling the hemolytic uremic syndrome of childhood. Renal biopsy demonstrated eosinophilic material in arterioles and capillaries. There was no fibrinoid necrosis or cellular proliferation. At autopsy the small arteries contained subendothelial fibrinlike occlusive thrombi, and the authors commented on the similarity of TTP lesions to the generalized Shwartzman reaction, in which hyaline and fibrinlike thrombi exist. The presence of these thrombi in afferent arterioles, or especially the glomerular capillaries, could lead to acute renal failure and renal cortical necrosis.

TTP associated with severe renal abnormalities may be difficult to differentiate from Gasser’s hemolytic uremic syndrome.⁵ His patients were children under one year of age whose symptoms followed acute gastroenteritis or upper respiratory infection. Progressive anemia, thrombocytopenia, cerebral symptoms, and rapidly deteriorating renal functions occurred. At autopsy, five children had renal cortical necrosis, and one case resembled TTP with thrombotic lesions. It should be added that neurologic symptoms have been described without associated vascular lesions at autopsy.
A Case of Renal TTP

Somewhat similar are cases reported by Shumway and Miller, and Allison and Dacie. Shumway's cases had antecedent infections, and the irregular contracted red cell morphologic changes occurred during hemolysis. There was no noticeable correlation between degree of azotemia and red blood cell morphology. A diagnosis of TTP was suggested but never supported histologically. The renal changes simulated acute glomerulonephritis, whereas those of Gasser had bilateral renal cortical necrosis. One of five had vascular lesions of TTP. Children reported by Allison were also under 12 months of age and two of eight who died were found at autopsy to have TTP.

Identical morphologic red cell alterations and vascular lesions make it difficult to separate clearly TTP and hemolytic uremic syndrome. As suggested by Liebermann, only the repetitious clinical pattern seems valid. It must be recalled, however, that not all hemolytic uremic syndromes end in death; some children survive. This further narrows the clinical picture between TTP and hemolytic uremic syndrome because TTP has been known to be chronic and recurrent, but inevitably fatal.

In differential diagnosis, SLE must be considered. Generally we think of TTP as having a predilection for young females in the 20 to 30-year age group, who also manifest an allergic background so commonly associated with collagen diseases like systemic lupus erythematosus and periarteritis. Our patient, however, had no known allergies and was in excellent health prior to this fulminating illness of one month's duration.

Review of histologic material by Levine and Shearn demonstrated 23% of 151 cases of TTP had coexisting SLE. They suggest that the altered vascular and immunologic response of SLE may predispose to the development of TTP. The question is raised as to whether the fibrinoid material of SLE is identical to the thrombotic plugs of TTP. These authors commented on fibrin and red blood cell deposition in afferent arterioles and glomerular capillaries, in addition to "onion skin" arteriolar changes in the spleen. Proteinuria, hematuria, pyuria and casts were present.

Not only may TTP be associated with collagen disease such as SLE, but it may have a familial incidence. TTP in siblings has been reported recently by Norkin et al. Both of their cases shared clinical and pathological features of SLE, but had TTP terminally with a mixture of histologic renal abnormalities such as the case described by Ramkissoon.

The pathogenesis of TTP is poorly understood. Since the original descriptions of hyaline thrombi occluding the arterioles and capillaries, there have been conflicting views on the source of these thrombi. What, if any, role has the vessel wall in initiating symptoms of this disease? Subintimal deposits of PAS positive material and aneurysmal dilatation of vessels at the arteriocapillary junction have been described in many organs. The once proposed plug of red blood cells or platelets has been disproved by the immunofluorescent demonstration by Craig and Gitlin that these thrombi contain fibrin, fibrinogen or its derivatives. Herein lies another possible
etologic consideration in TTP — that of intravascular coagulation or defibrination with features similar to other such clinical states. Histologic descriptions of fibrin in the renal tubules and reports of hypofibrinogenemia, hypoprothrombinemia, and thrombocytopenia, all favor accelerated intravascular coagulation in TTP.

Review of the autopsy in our patient showed extensive vascular thrombosis in the kidneys, adrenals, heart and brain. The kidney was most severely involved. The lumen of glomerular capillaries, arterioles and small arteries, and less frequently their walls, contained a homogeneous eosinophilic material which sometimes had evoked an endothelial cell proliferation (Figures 1 and 2). These stained red with the Masson trichrome stain, strongly PAS positive with and without diastase digestion, and were not argyrophilic with Jones stain. In general they were homogeneous acid. Only rarely were strands of fibrin visible (Figure 3A). Recent small infarcts were commonly encountered in association with the occluded vessels (Figure 4).

Within the viable renal parenchyma, tubular dilatation and frequent homogeneous and granular casts were present, sometimes containing fibrin (Figure 3B). The epithelial cells of a number of tubules were flattened against the basement membrane, while in others the cells were swollen and contained a clear cytoplasm.

Glomerular tufts sometimes had an accentuated lobular pattern with focal thickening of the basement membrane. This on occasion formed a striated mass.
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Figure 4
One of many small hemorrhagic infarcts (A) resulting from thrombotic arteriole and arteriolar occlusion (B).
H & E x 300

which obliterated the capillary lumen (Figure 5). Focal endothelial and epithelial cell proliferation was frequently associated with basement membrane changes, and also seen independently. Red cells, granular and homogeneous material and (rarely) strands of fibrin were sometimes observed in Bowman’s space. Adrenal necrosis was noticeable and associated with small and large vascular thrombi.

The cardiac conducting system vascular changes have been previously described. They were unique in that the working myocardium, with the exception of one area near the mitral valve, was not affected in the sections studied.

Histologic lesions formed in TTP simulate, in some respects, those described in the generalized Shwartzman reaction in experimental animals. These animals develop intravascular thrombi as a result of hypercoagulability and may develop renal cortical necrosis, hyaline and fibrinlike thrombi.

Coagulation Profile
Complete coagulation profile and immunofluorescent tissue studies of bone marrow, liver, spleen and lymph node were done on our patient. Summarized data appear in Tables I and II.
Focal glomerular basement membrane thickening is best seen in glomerulus (A). Thrombi in arterioles and glomerular capillaries (B) are not stained by the silver.  
Jones Silver Methenamine stain x 300

The prolonged recalcification time, partial thromboplastin time and one-stage prothrombin time could suggest a deficiency of prothrombin and procoagulants, Ac-globulin and factor VIII, since these tests depend to some extent on the production of thrombin from its precursor prothrombin.

Addition of thrombin to plasma in the thrombin time test illustrated that adequate amounts of fibrinogen were present for fibrin formation. Actually, the excessive amounts of fibrinogen, evidenced by an excess of 2-4 standard deviations, suggest that the liver was in an accelerated synthesis phase. Other plasma proteins were normal on 8/23/65, but were low on 8/24/65.

There was no direct evidence that systemic fibrinolysis was active on 8/24/65 as the euglobulin lysis time was not shortened, the profibrinolysin level was in the normal range on 8/23/65 and 8/24/65, and the fibrinogen level was high on 8/24/65. On 8/23/65, however, a specific immunologic test demonstrated elevated nonclottable fibrinogen related molecules. This test illustrates either that systemic lytic activity had been present or that local fibrinolysis existed, because the protein degradation products of fibrinolysis were evident. Normally, the liver reticuloendothelial cell clears these products from the circulation. These degradation products were not cleared, sug-
### A Case of Renal TTP

#### Table I

Cellular Fluorescence as an Indicator of Specific Protein Localizations

<table>
<thead>
<tr>
<th>Proteins</th>
<th>Cell Types and Locations</th>
<th>Normal Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>Hepatocytes</td>
<td>80-90%</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>Hepatocytes</td>
<td>&lt;50%</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Hepatocytes</td>
<td>&lt;5%</td>
</tr>
<tr>
<td></td>
<td>Liver Macrophages</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Spleen Macrophages</td>
<td>Rare</td>
</tr>
<tr>
<td>Blood Neutrophils</td>
<td>[8/20, 8/24 AM, 8/24 PM]</td>
<td>Numerous</td>
</tr>
<tr>
<td></td>
<td>Bone Marrow Neutrophils</td>
<td>0</td>
</tr>
<tr>
<td>Gamma Globulin</td>
<td>Lymph Node Lymphocytes</td>
<td>Some</td>
</tr>
<tr>
<td></td>
<td>Spleen Lymphocytes</td>
<td>Rare</td>
</tr>
<tr>
<td>Platelet Material</td>
<td>Blood Platelets</td>
<td>Present</td>
</tr>
<tr>
<td></td>
<td>Bone Marrow Megakaryocytes</td>
<td>Present</td>
</tr>
<tr>
<td></td>
<td>Liver Macrophages</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Spleen Macrophages</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Table II

COAGULATION AND FIBRINOLYTIC STATUS

<table>
<thead>
<tr>
<th>TEST</th>
<th>PATIENT SAMPLES</th>
<th>CONTROL RANGE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recalcification Time (Sec)</td>
<td>8/23 Serum</td>
<td>80 - 120</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Partial Thromboplastin Time (Sec)</td>
<td>8/24 A.M. Plasma</td>
<td>8/24 P.M. Plasma</td>
<td>50 - 90</td>
</tr>
<tr>
<td>One-Stage Prothrombin Time (Sec)</td>
<td>22.3</td>
<td>12.8</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Prothrombin (U/ml)</td>
<td>40</td>
<td>162 ± 20</td>
<td>Low</td>
</tr>
<tr>
<td>Ac-globulin (U/ml)</td>
<td>3.1</td>
<td>49.5</td>
<td>Low</td>
</tr>
<tr>
<td>Factor VIII (%)</td>
<td>84</td>
<td>60 - 200</td>
<td>Marginal</td>
</tr>
<tr>
<td>Thrombin Time (Sec)</td>
<td>7.1</td>
<td>11.2</td>
<td>Shortened</td>
</tr>
<tr>
<td>Fibrinogen (mg%) Thrombin Clottable</td>
<td>0</td>
<td>525</td>
<td>174 ± 71</td>
</tr>
<tr>
<td>Fibrinogen (mg%) Heat Precipitable</td>
<td>0</td>
<td>385</td>
<td>174 ± 71</td>
</tr>
<tr>
<td>Non-clottable (serum) Fibrinogen-Related Molecules (mg%)</td>
<td>320</td>
<td>80</td>
<td>20 - 60</td>
</tr>
<tr>
<td>Profibrinolsin (U/ml)</td>
<td>99</td>
<td>119</td>
<td>107 ± 12.5</td>
</tr>
<tr>
<td>Euglobulin Lysis Time (Min.)</td>
<td>&gt;360</td>
<td>&gt;180</td>
<td>Fibrinolysis not present</td>
</tr>
<tr>
<td>Whole Blood Clot Time (Min.)</td>
<td>6</td>
<td>5 - 10</td>
<td>Normal</td>
</tr>
<tr>
<td>Total Protein (g%)</td>
<td>5.6</td>
<td>4.3</td>
<td>Low on 8-23</td>
</tr>
</tbody>
</table>

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gesting that these RE cells are occupied with other clearance duties (i.e., platelet aggregates or small thrombi). Another feasible explanation is that localized fibrinolysis from generalized intravascular sites contributes fibrin degradation products faster than the RE cells can clear them.

**Protein Synthesis**

Elevated synthesis of blood coagulation proteins, prothrombin and fibrinogen by the liver RE cells was noted in this patient from the study of cellular fluorescence. Albumin synthesis and storage by the liver appears reduced. Possibly there is already maximum capacity of protein synthesis of other blood clotting proteins, or maybe albumin loss or utilization in circulation has exceeded normal albumin production. Gamma globulin synthesis and storage by lymphocytes and plasma cells appeared reduced, which may reflect either impaired synthesis or excessive demands for production.

**Reticuloendothelial Clearance**

There is evidence of excessive phagocytosis of fibrin-related material. The liver and spleen macrophages are engaged in clearing circulating fibrin deposits, platelet aggregates and small thrombi, since these cells are degradation sites.

As mobile defenders against fibrin deposits neutrophils were especially active early, as shown by prominent cell fluorescence during the period from 8/20 to the morning of 8/24. By the evening of 8/24 there was reduced neutrophil fluorescence and content of fibrinogen-related material. This could indicate that intracellular digestion was completed, or that intravascular plugging was extensive, thus preventing neutrophils from getting into thrombi to exert their phagocytic action. Previous phagocytic work might deplete proteolytic enzymes which are necessary for the digestive phase of phagocytosis. An alternate explanation could be bone marrow depression with the reduced delivery of neutrophils or release of cells too immature to function effectively in thrombolytic mechanisms.

Fluorescent studies of the RE cells of the liver and spleen demonstrated platelet phagocytosis. It is interesting to note halos of fibrinogen-related material coating the red blood cells and platelets.

There are similarities between some of these data and those previously described in another fatal case of TTP. Normally, only trace amounts of fibrin split products are formed in normal serum. Thus, the presence of fibrin in the blood vessels, or the presence of large quantities of circulating split products, is evidence for the presence of intravascular coagulation.

As proposed by R. N. Taub et al in an interesting editorial, TTP can be compared with other defibrination syndromes and perhaps with the generalized Shwartzman reaction in animals, where fibrin is present in association with altered coagulation and deposition of intravascular fibrin.
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In our patient, fibrin was found in the renal tubules. Cellular fluorescent study gave evidence to suggest impaired RES clearance of fibrin permitting it to accumulate intravascularly. Lee\textsuperscript{10} describes a similar mechanism in the generalized Shwartzman reaction.

Both hypofibrinogenemia\textsuperscript{20} and increased fibrinogen\textsuperscript{21} have been described in TTP. Either result is possible, depending on the exact phase of reticuloendothelial protein synthesis or RES clearance, and on utilization of fibrinogen and fibrin-related materials.

If defibrination does occur with deposition of intravascular fibrin, as suggested by Taub,\textsuperscript{18} then the anemia and thrombocytopenia of TTP can be logically explained. Fibrin deposits in small blood vessels would also serve as mechanical factors capable of producing the morphologic fragmentation forms and microspherocytes and schistocytes described by Brain et al\textsuperscript{12} in microangiopathic hemolytic anemia. The presence of vasculitis is not necessary as TTP is usually not associated with vasculitis unless there is coexistent collagen disease.

Summary

The renal aspects of TTP have been described with particular reference to the similarity between acute glomerulonephritis, hemolytic uremic syndrome and TTP. Coagulation parameters and immunofluorescent tissue studies are presented. This data is presented, in part, as further support for the proposed etiologic theory of intravascular coagulation in TTP and its resemblance to the generalized Shwartzman reaction.

REFERENCES


