Deficiency of Plasma Protein S, Protein C, or Antithrombin III and Arterial Thrombosis

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Protein C and protein S are vitamin K-dependent coagulation factors that together act as an anticoagulant, and antithrombin III is a plasma protein that inhibits several activated factors in the coagulation cascade. Although deficiencies of any of these three proteins have been associated with venous thrombosis, arterial thrombosis has not been prominently associated with deficiencies of these factors. We report one patient with a protein S deficiency, another with a protein C deficiency, and a third with an antithrombin III deficiency, each of whom had extensive arterial thrombosis. We suggest that deficiencies of these proteins may constitute risk factors for arterial thrombosis. (Arteriosclerosis 7:456–462, September/October 1987)

Protein C and protein S are vitamin K-dependent plasma proteins that together have an anticoagulant function. The enzymatically active form of protein C (activated protein C) inhibits the clotting cascade at the levels of factors V and VIII, and protein S serves as a cofactor in these reactions. Previous studies demonstrated a predisposition to recurrent venous thrombosis in individuals congenitally deficient in either protein C, or protein S. To date, there has been a striking absence of arterial thrombosis reported in such individuals, although one protein C-deficient patient and one protein S-deficient patient suffered myocardial infarctions in the fourth decade of life, and one protein C-deficient patient had a femoral artery thrombosis antedating the onset of venous thrombosis. Antithrombin III (AT-III) is a plasma protein that inhibits several of the serine proteases involved in the coagulation cascade; heparin greatly accelerates its rate of inhibition. Hereditary deficiency of AT-III has also been associated with a marked predilection to venous thrombosis, but arterial thrombosis has only rarely been connected with this deficiency. We now report data on three unrelated men, one deficient in protein S, one deficient in protein C, and one deficient in AT-III, all of whom experienced well-documented arterial thromboses. The protein S-deficient man had extensive venous and arterial thrombosis affecting the lower extremities, renal arteries and veins, and aorta. The protein C-deficient man had recurrent deep vein thrombosis, pulmonary embolus, and a left ventricular thrombus that led to occlusive emboli in the femoral, radial, ulnar, and left anterior descending coronary arteries; this last embolus resulted in a myocardial infarction. The AT-III-deficient man had three separate episodes of thromboemboli originating from his heart and affecting his lower extremities, but he has not had any venous disease.

Methods

Blood counts and chemistries, prothrombin time (PT), partial thromboplastin time (PTT), Veneral Disease Research Laboratory test for syphilis (VDRL), antinuclear antibody, latex fixation, direct and indirect antiglobulin tests, complement assays, and erythrocyte sedimentation rates were performed by standard laboratory techniques. Platelet aggregation in response to adenosine diphosphate (ADP), epinephrine, and soluble collagen was studied as previously described. Sensitivity was assessed by lowering the concentration of the agonist until a response was not obtained. A control sample was tested at the same time. Von Willebrand factor antigen was measured by electroimmunoassay, and ristocetin cofactor was measured with lyophilized platelets (Bio/Data Corporation, Hatboro, Pennsylvania). Plasminogen was measured by radiointumodiffusion (M-Partigen, Behring Diagnostics, La Jolla, California). AT-III was measured immunologically by radial immunodiffusion or by electroimmunoassay. Crossed immunoelectrophoresis of AT-III was measured as previously described by Huftlin. Functional AT-III was measured by a chromogenic substrate assay (Diacron AT-III, Wellcome Diagnostics, Greenville, North Carolina) using bovine thrombin in cases 1 and 2 and by measuring the kinetics of inhibition of pure human thrombin in defibrinated plasma in case 3. Human thrombin was purified as previously described. Immunologic protein C levels were measured by electroimmunoassay, and functional levels were measured with a chromogenic
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substrate after converting the protein C to its active form with a thrombin-thrombomodulin complex. Protein S antigen was measured by electroimmunossay, protein S functional activity was measured by its ability to act as a cofactor for activated protein C, and the relative amounts of free and bound protein S antigen were determined by crossed immunoelectrophoresis.

Patient 3's IgG was purified on an affinity column of protein A-Sepharose (Pharmacia, Placatway, New Jersey). The patient's plasma (3 ml) was mixed 1:3 with 0.1 M NaPO₄ (pH 8) and was applied to the column. After the first peak (peak 1) was eluted, the buffer was changed to a low pH buffer (Bio-Rad elution buffer, Richmond, California), and the IgG was eluted (peak 2). These latter fractions were immediately neutralized with 1 M Tris/Cl (pH 7.0). The peaks were pooled and dialyzed against 0.1 M NaCl, 0.01 M Tris/Cl (pH 7.4). Peak 1 had an OD₂₈₀ = 7.49. Peak 2 was concentrated in a membrane concentrator (Minicon B-15, Millipore, Bedford, Massachusetts) to an OD₂₈₀ = 6.25. SDS-polyacrylamide gel electrophoresis confirmed the purity of the IgG, with only minor contaminants. Patient and control IgG fractions were also purified by ion-exchange chromatography using a Zetachrome disk (Amicon, Meriden, Connecticut) according to the manufacturer's directions. Fractions were dialyzed against 0.15 M NaCl, 0.01 M Tris/Cl (pH 7.4) and then concentrated to an OD₂₈₀ of 6.60 (control IgG) and 7.87 (patient IgG) using an immersible filter concentrator (CX-10 ultra filter, Millipore). Patient 3's plasma (2.7 ml) was also chromatographed on a 95 by 1 cm column of Sephacryl S-200 (Pharmacia) at 5 ml/hr using an elution buffer of 0.15 M NaCl, 0.01 M Tris/Cl, and 0.05% azide (pH 7.4). Fractions eluted from the column were tested for OD₂₈₀, immunologic AT-III content, immunologic IgG content, and the ability to inhibit the thrombin time of normal plasma. Thrombin times were performed in a semi-automated system (fibrometer, BBL, Cockeysville, Maryland) by warming 0.1 ml of 0.15 M NaCl, 0.01 M Tris/Cl (pH 7.4), and 0.1 ml of plasma to 37° C for 3 minutes and then adding 0.1 ml of a 1.8 U/ml solution of bovine thrombin (Parke-Davis, Morris Plains, New Jersey). Factor assays were performed with factor-deficient substrate plasmas using an automated optical end-point instrument (Coag-A-Mate, General Diagnostics, Morris Plains, New Jersey).

Protein S-Deficient Patient

Case History

The patient first developed pain, swelling, and erythema of his left calf at age 16, several weeks after a minor motorcycle accident. Over the next 2 to 3 years he had several such incidents involving both legs; at least two incidents were accompanied by hemothrosis and chest pain. At age 19 he had stasis ulcers of his right leg, and a venogram documented obliteration of the deep venous system. He was started on warfarin, but over the next year his regimen was changed repeatedly as he developed complications (retroperitoneal hemorrhage) and recurrent venous thromboses involving his upper and lower extremities. During one episode, he was thought to have pulmonary embolism while on heparin and so an inferior vena cava clipping was performed. Biopsies of both lower extremities showed thickened vein walls and chronic perivascular inflammation, but no evidence of acute vasculitis. Ultimately, the patient developed hematuria and right flank pain while on heparin, warfarin, and aspirin. An angiogram showed probable thrombosis of an upper right renal vein but there was normal arterial flow to both kidneys.

At age 21 the patient began to experience thrombotic arterial disease of the right leg. A thrombectomy failed to stop the progression of the insufficiency and so the leg was amputated below the knee. The surgical specimen revealed organizing thrombus in both arteries and veins without evidence of vasculitis. Subsequent arterial insufficiency in the left leg led to the insertion of an aorto-iliofemoral bypass graft, but the graft occluded and at age 23 the leg was amputated below the knee in order to control his pain. He remained stable for the next 4 years on subcutaneous heparin (8,000 U q8h), but he then developed headaches and was found to be severely hypertensive (232/148). A renal scan and digital subtraction angiogram demonstrated the absence of perfusion to a shrunken left kidney and perfusion of the right kidney only by the upper artery, the lower one being occluded (Figure 1). In addition, the aorta was obstructed at the level of the renal hilum. A repeat skin biopsy revealed mild perivascular mixed cell inflammation and mural thickening of the vessel walls (Figure 2); no immunoglobulin, complement, fibrinogen, or properdin was detected in the vessel by fluorescent microscopy and there was no evidence of microabscess formation. The patient was restarted on warfarin and an empiric trial of plasmapheresis was begun; the latter was discontinued, however, when an arteriovenous graft clotted. At approximately the same time, the patient stopped smoking (he had begun at age 12), and he has remained stable on warfarin and antihypertensive medications for the past 2 years.

Family history includes two episodes of deep vein thrombosis in the patient's mother (J.K.), one postpartum and the other after hysterectomy. In addition, a sister (D.K.) had an episode of postpartum deep vein thrombosis at age 22. Both relatives have been asymptomatic and off therapy for many years.

Laboratory Data

Routine laboratory data, including blood cell counts, electrolytes, cholesterol, and triglycerides were all within normal limits. Urinalysis was unremarkable. VDRL, antinuclear antibody, latex fixation, direct and indirect antiglobulin tests, electrocardiogram, echocardiogram, urine homocysteine, and C3 were all within normal limits. The erythrocyte sedimentation rate was intermittently increased (6 to 43 mm/hour), the BUN and creatinine were borderline (25 and 1.7 mg/dl, respectively), and the creatinine clearance was only ~50 ml/min. The patient's platelets did not show increased sensitivity to aggregation induced by ADP, epinephrine, or soluble collagen. Assays of ristocetin cofactor, von Willebrand factor, factors V and VIII, fibrinogen, and plasminogen were all within normal limits.

Table 1 contains the results of the assays for AT-III,
protein C, and protein S. AT-III and protein C levels were normal. Although the immunologic protein S value was normal, the functional protein S value was markedly reduced, and this was confirmed by the absence of a free peak of protein S by crossed immunoelectrophoresis (Figure 3). The results of the functional protein S determinations and the crossed-immunoelectrophoreses on the patient's family members are also reported in Figure 3. The propositus' sample was obtained while he was on heparin; two other samples obtained while he was on warfarin showed even more profound decreases in functional activity. The other family members were not taking any medica-

Figure 1. Digital subtraction angiogram of the aorta and its branches. An irregular occlusion of the aorta is noted at the level of the renal hila. There are no vessels supplying the left kidney and only one of two right renal arteries is patent, supplying the upper pole of the kidney. No magnification.

Figure 2. Biopsy of blood vessel from protein S-deficient patient showing mild perivascular inflammation and mural thickening of the vessel walls. The slide was stained with hematoxylin and eosin. × 400
Protein C-Deficient Patient

Case History

The patient is a native of Belize who has lived in the United States since age 18 and smokes one-half pack of cigarettes per day. At age 23 he developed the first of three episodes of deep venous thrombosis documented by venography. At age 27 a fourth episode of deep venous thrombosis was complicated by angiographically documented pulmonary embolism, but he was lost to follow-up after initial heparin and warfarin therapy. At age 31, 6 weeks after he self-discontinued warfarin therapy, the patient developed angiographically documented left radial and ulnar artery occlusions. High-speed CT scanning of the heart was consistent with a ventricular thrombus. Another left leg embolus occurred while the patient was hospitalized, but his heparin level was subtherapeutic at that time. Resection of the mass was not undertaken, and the patient was discharged on warfarin and diprydamole. Echocardiography 2 months later revealed disappearance of the ventricular mass, and the patient has had no further thromboembolic events after a year of follow-up.

Laboratory Data

The patient's blood counts were all within normal limits on four separate occasions. His preheparin partial thromboplastin time was within normal limits. Repeated antinuclear antibody determinations were negative. Immunologic and functional AT-III and plasminogen levels were normal in the patient and his mother. The patient's protein C level while on stable warfarin therapy was markedly reduced by both functional and immunologic methods; when analyzed in comparison to the patient's factor IX antigen by the method of Griffin et al., the patient's value was approximately 0.33, indicating that he is heterozygous deficient for protein C. When the patient has had no further thromboembolic events after a year of follow-up.

Table 1. Laboratory Values in Three Patients

<table>
<thead>
<tr>
<th>Protein S</th>
<th>Protein C</th>
<th>Antithrombin III</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.6 mg/dl (17 to 30)</td>
<td>95%</td>
<td>15 mg/dl (22 to 39)</td>
</tr>
<tr>
<td>105%</td>
<td>100%</td>
<td>0.9/min (2.7/min)</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Factor IX antigen (% normal)</td>
<td>Protein C</td>
<td>Protein S</td>
</tr>
<tr>
<td>92</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>Immunologic (% normal)</td>
<td>Immunologic (% normal)</td>
<td>Immunologic (% normal)</td>
</tr>
<tr>
<td>103</td>
<td>20</td>
<td>53</td>
</tr>
<tr>
<td>Functional (% normal)</td>
<td>Functional (% normal)</td>
<td>Functional (% normal)</td>
</tr>
<tr>
<td>98</td>
<td>33</td>
<td>—</td>
</tr>
<tr>
<td>Ratio protein C/factor IX Ag</td>
<td>Ratio protein C/factor IX Ag</td>
<td>Ratio protein C/factor IX Ag</td>
</tr>
<tr>
<td>1.12</td>
<td>0.33</td>
<td>1.05</td>
</tr>
<tr>
<td>Immunologic (% normal)</td>
<td>Immunologic (% normal)</td>
<td>Immunologic (% normal)</td>
</tr>
<tr>
<td>102</td>
<td>100</td>
<td>53</td>
</tr>
<tr>
<td>Functional (% normal)</td>
<td>Functional (% normal)</td>
<td>Functional (% normal)</td>
</tr>
<tr>
<td>22</td>
<td>83</td>
<td>—</td>
</tr>
<tr>
<td>Ratio protein S/factor IX Ag</td>
<td>Ratio protein S/factor IX Ag</td>
<td>Ratio protein S/factor IX Ag</td>
</tr>
<tr>
<td>1.11</td>
<td>1.64</td>
<td>0.88</td>
</tr>
</tbody>
</table>

*Tested while patients were taking warfarin.
†Antithrombin III immunologic values for the protein S- and antithrombin III-deficient patients are reported as mg/dl with the normal range given in parentheses, whereas the immunologic value for the protein C-deficient patient is expressed as the % of a normal plasma pool. The functional assay results are expressed as % of a normal plasma pool for the protein S- and protein C-deficient patients, and as the thrombin neutralization rate for the antithrombin III-deficient patient, with the value for a simultaneously assayed normal individual given in parentheses.

at the time of blood drawing. The propositus' brother, K.K., had a normal functional assay and a normal crossed immunoelectrophoresis pattern, with the two peaks containing protein S complexed with C4b binding protein and free protein S, respectively. In contrast, all of the other family members had markedly reduced functional protein S activity and abnormal crossed immunoelectrophoresis patterns showing only the bound protein S peak and virtually no free protein S. Total protein S antigen was normal in all of the family members (mother's value 60% and children's values, from left to right in Figure 3, 66%, 57%, 55%, 96%, and 49%). The normal range, determined in 21 individuals, is 48% to 152%. Thus, the protein S deficiency in this family, like that reported in other families, involves a marked decrease in free protein S, the only form that is active as a cofactor for protein C.
Fraction 2 contained the eluted IgG at OD^260 = 6.3.

Table 2. Thrombin Times of Control Plasma, Plasma from Antithrombin III-Deficient Patient, and Control Plasma in Presence of Patient IgG

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Plasma</th>
<th>Bovine thrombin</th>
<th>Human thrombin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patient</td>
<td>&gt;120</td>
<td>23.8</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>30.6</td>
<td>23.9</td>
</tr>
<tr>
<td></td>
<td>Patient + Control (1:1)</td>
<td>&gt;120</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>34.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Control + Patient Fx 1* (1:1)</td>
<td>34.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control + Patient Fx 2* (1:1)</td>
<td>74.0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Control</td>
<td>66.6</td>
<td>61.2</td>
</tr>
<tr>
<td></td>
<td>Patient</td>
<td>&gt;170</td>
<td>61.3</td>
</tr>
<tr>
<td></td>
<td>Control + Patient IgG† (1:1)</td>
<td>163.9</td>
<td>77.4</td>
</tr>
<tr>
<td></td>
<td>Control + Buffer (1:1)</td>
<td>66.9</td>
<td>72.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bovine Thrombin (U/ml)</th>
<th>Patient times</th>
<th>Control times</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>&gt;600</td>
<td>71.4</td>
</tr>
<tr>
<td>1.0</td>
<td>&gt;600</td>
<td>29.4</td>
</tr>
<tr>
<td>2.1</td>
<td>20.9</td>
<td>18.0</td>
</tr>
<tr>
<td>4.2</td>
<td>8.9</td>
<td>7.6</td>
</tr>
<tr>
<td>8.3</td>
<td>5.4</td>
<td>5.2</td>
</tr>
<tr>
<td>16.7</td>
<td>3.4</td>
<td>3.3</td>
</tr>
</tbody>
</table>

*AFraction 1 contained the flow through peak (depleted of IgG) of the protein A affinity column at an OD^260 = 7.5. Fraction 2 contained the eluted IgG at OD^260 = 6.3.
†Patient and control IgG were purified by ion-exchange chromatography and concentrated to OD^260 = 7.9 and 6.6, respectively.

Antithrombin III-Deficient Patient

Case History

A 15-year-old white man noted the onset of pain and numbness in his right leg, and an evaluation revealed obstruction of the right femoral artery with evidence of multiple defects suggesting an embolic episode. Surgical removal of the thrombosis restored function to the leg. A systolic heart murmur was noted and echocardiography revealed prolapse of the mitral valve and an unusual echogenic area are just below the aortic valve. Subsequent cardiac catheterization confirmed the mitral valve prolapse and demonstrated a bicuspid aortic valve with aortic stenosis. The patient was placed on warfarin for several months and was then switched to aspirin. At age 16 the patient developed a similar episode in the left leg and angiography confirmed the presence of a left femoral artery thromboembolus. The obstruction was surgically corrected and the clinical response was good. One month later the patient underwent open heart surgery, at which time a thrombus was noted in a cul-de-sac under a large common anterior aortic cusp; the latter prolapsed into the left ventricle during diastole, producing an area of blood stasis. A subvalvular fibrous ring was identified and resected. There was no histologic evidence of bacteria in the clot or resected segment. The patient remained well on warfarin for the next 3 years, but then again developed pain and numbness in the left leg, and angiography confirmed the presence of obstruction of the left femoral artery. A prothrombin time performed several days before this episode was within the normal range, indicating inadequate anticoagulation. Surgical intervention again relieved the symptoms, and the patient currently remains well on warfarin, 5 months after this last episode. The patient never smoked. The patient's father and mother were both asymptomatic and had no history of thrombotic disease.

Laboratory Data

Routine laboratory data, including blood cell counts, lipids and blood glucose were all within normal limits. Routine coagulation data, including PT, PTT, and fibrinogen, were normal when the patient was not taking warfarin. Plasminogen, factor V, and factor VIII were all within normal limits. Protein S and protein C antigen values were determined while the patient was on warfarin; the absolute values (53% and 63%, respectively) were low compared to individuals not taking warfarin, but were within the normal range when normalized for the patient's factor X antigen (60%) (Table 1). The patient's protein S pattern on crossed-immunoelectrophoresis was normal. AT-III was 15 mg/dl (normal 22 to 39) while on warfarin, was 8.9 mg/dl. The patient's PTT did become prolonged on heparin, going from 28.6 sec to as much as 70.1 sec. Three years later, the immunologic AT-III was 15 mg/dl (normal 17 to 30 mg/dl) and the second, obtained 3 days later while the patient was on warfarin; the absolute values measured immunologically on two specimens at the time of surgery in 1983; the first was obtained just before heparinization and was found to be 12.5 mg/dl (normal 17 to 30 mg/dl) and the second, obtained 3 days later while the patient was on heparin, was 8.9 mg/dl. The patient's PTT did become prolonged on heparin, going from 28.6 sec to as much as 70.1 sec. Three years later, the immunologic AT-III was 15 mg/dl (normal 22 to 39) while on warfarin, and the functional AT-III was diminished when tested against purified human thrombin (Table 1). Crossed-im-
munoephrophoresis revealed a diminished amount of AT-III antigen of normal migration in both the absence and presence of heparin. The patient's mother had an immunologic AT-III of 11.4 mg/dl and reduced functional AT-III, whereas the father's AT-III was normal (30 mg/dl). Interestingly, the patient was found to have a normal thrombin time using human thrombin at all concentrations, but an infinite thrombin time using bovine thrombin at <1 U/ml (Table 2). The patient's plasma contained a thrombin time-inhibitor that chromatographed with his IgG by Sephacryl S-200 chromatography, protein A Sepharose affinity chromatography, and ion exchange chromatography; the inhibitor was clearly separate from his AT-III (Table 2).

Discussion

The severity of the arterial disease in these three patients is very striking, raising the possibility that it is related to the deficiencies of protein S, protein C, and AT-III, respectively. At present we have no explanation for why these patients have had arterial thrombosis, whereas other affected members of the families have had venous thrombosis or are asymptomatic; possibilities include the presence of another, underlying arterial disease or additional predisposing factors, such as male sex, trauma, or cigarette smoking. Cigarette smoking may well have contributed to the vascular disease in the protein S-deficient patient because there was a dramatic halt in the progression of his disease when he stopped smoking. This association of severe arterial disease with smoking in a young man raises the possibility of Buerger's disease, but several features of this patient's disease are uncharacteristic of the classic form of that disorder: 1) Buerger's disease usually affects the veins as a result of arterial disease, whereas our patient suffered venous disease long before arterial disease; 2) Buerger's disease affects the medium and small arteries predominantly, whereas our patient had large artery involvement from the beginning; and 3) none of the histologic lesions characteristic of Buerger's disease (the early lesions of microabscesses within thrombi with giant cells, or the late lesions of fibrosing granulomas) could be identified. Given the pleiotropic nature of Buerger's disease, however, we cannot conclusively exclude this diagnosis. It would be useful, therefore, to test patients with the classic features of Buerger's disease for protein S deficiency.

The AT-III-deficient patient is most unusual in that, despite having arterial disease, he has had no evidence of venous disease. His inhibitor to bovine, but not human, thrombin appears to be an acquired abnormality unrelated to his inherited AT-III deficiency. A similar inhibitor was recently described in an asymptomatic patient who had been exposed to topical bovine thrombin; no such exposure could be documented with our patient. One striking similarity between the protein C deficient-patient and the AT-III-deficient patient was that both had thromboembolus originating from the heart. It may well be that areas of the heart with retarded blood flow behave like venous sites in being predisposed to thrombosis by these congenital protein deficiencies. In fact, a previous patient with AT-III deficiency died of massive intracardiac thrombosis. The development of deep vein thrombosis in the protein S-deficient patient's mother and sister during pregnancy may be of clinical significance since we have found that pregnancy in normal women is associated with an acquired protein S deficiency, characterized by reduced immunologic levels of free protein S and significantly reduced protein S functional activity. Others have also reported the initial onset of venous thrombosis in protein S-deficient women during pregnancy.

These cases suggest that it may be premature to conclude that there is an absence of arterial disease in protein S, protein C, and AT-III deficiency, especially with regard to thromboemboli originating in the heart. Given the complexity of vascular disease, it is more reasonable to suspect that they are risk factors rather than truly causative. We conclude that assays of these proteins should be performed on patients with extensive arterial thrombosis, especially if there is a family history of either venous or arterial disease.

Note added in proof: Since submission of this manuscript, a review of arterial thrombosis and inhibitors of coagulation has been published that reinforces the likely association between arterial thrombosis in a small minority of patients with differences in either AT-III or protein C. In addition, a brief report of arterial thrombosis in a patient with AT-III deficiency came to our attention.

Acknowledgments

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References


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