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Thrombotic Thrombocytopenic Purpura Causing Sudden, Unexpected Death—A Series of Eight Patients

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ABSTRACT: Eight patients were presented to the medical examiner after dying suddenly and unexpectedly from thrombotic thrombocytopenic purpura. Compared with patients who die after prolonged hospitalization and treatment, these patients showed fewer neurologic symptoms and correspondingly fewer or no microthrombi within the brain. Only four of eight subjects developed fever, which further contributed to misdiagnosis. The differences in clinical presentation between our cases and most published series is striking and may be explained by shorter duration and no treatment. Each case contained the characteristic histology of thrombotic thrombocytopenic purpura. Ischemic injury to the heart and conduction system was the most likely mechanism of sudden death. Included in this series is a patient with acquired immunodeficiency syndrome (AIDS) diagnosed at autopsy, a concurrence that is now appearing more frequently in the medical literature.

KEYWORDS: pathology and biology, death, thrombotic thrombocytopenic purpura, microthrombi, natural death, sudden death

Thrombotic thrombocytopenic purpura (TTP) is an acute diffuse disorder of the microcirculation characterized by thrombocytopenic purpura, microangiopathic hemolytic anemia, transient and fluctuating neurologic signs, renal dysfunction, and a febrile course [*1*]. This definition is based on hospitalized and treated patients. Although TTP is sometimes suddenly fatal, patients usually succumb after a variable hospital stay. Only case reports attest that TTP causes sudden and unexpected death—to our knowledge, no published series to date addresses this facet [*2–4*]. Thus, we examined seven cases of TTP that presented as sudden and unexpected death to the Dade and Broward Medical Examiner's Offices between 1982 and 1987. An additional case came from the Rochester Medical Examiner's Office.

Materials and Methods

We screened all deaths categorized as natural which had been autopsied by the medical examiner during 1982 to 1987 in Broward and Dade Counties of Florida for cases of, or

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suspicion of, TTP. During this period the average population was 3.0 million and the Medical Examiner's office completed 14 600 autopsies of persons dying of natural causes. Two of the eight cases were misdiagnosed, even after gross and microscopic examinations. They were signed out as idiopathic thrombocytopenic purpura and autoimmune disease, respectively. One case presented to the Rochester Medical Examiners Office.

We define "sudden and unexpected death" as that occurring within 24 to 72 h after the onset of symptoms in a person with no previously known medical problems. We included two patients with symptoms lasting longer than three days, whose deaths were still unexpected considering the mild and nonspecific nature of their symptoms.

We reviewed all clinical and hospital records, autopsy protocols, and the hematoxylin- and eosin-stained microscopic slides of each case. We stained selected slides with periodic acid-Schiff and phosphotungstic acid hematoxylin.

We summarized the clinical, laboratory, and autopsy findings of all eight cases in the results section. We describe Case 2 in detail because of the rare concurrence of TTP and AIDS.

Case 2

A 31-year-old homosexual white man came to Jackson Memorial Hospital, Miami, with nausea, vomiting, chills, and fever for three days after eating shrimp. On the day of admission, he developed dark urine and petechiae on his eyelids. He denied intravenous drug use, but admitted to smoking cocaine and marijuana. He had been treated for syphilis in 1972 and 1983.

His blood pressure was 120/86 mmHg, temperature 99°F (37.2°C), respirations 18/min, and heart rate 92/min. Petechiae covered the eyelids and soft palate. He had no other skin lesions. The red tonsils were not enlarged. He had enlarged cervical lymph nodes. The lung and heart exam was normal. His liver and spleen were not palpable. His gentalia and extremities were unremarkable. He had no neurologic abnormalities.

The hemoglobin was 9.0 g; hematocrit 26%; platelet count 8K; and white blood count 5800 with 46% polys, 14% bands, 31% lymphs, 4% monos, 1% eosinophils, and 4% basophils. His prothrombin time and partial thromboplastin time were 9.8 s (up to 14 s) and 29 s (up to 45 s), respectively. The reticulocyte count was 6.1%, and his peripheral blood smear showed "moderate anisocytosis and poikilocytosis." The urine contained 10 to 25 red blood cells/high-power field (HPF), 1 to 5 white blood cells/HPF, 5 to 10 granular casts/HPF and 3+ protein. Serum sodium was 137 mEq/L, potassium 4.2 mEq/L, chloride 103 mEq/L, and carbon dioxide content 25 mEq/L. His serum creatinine and blood urea nitrogen were 1.4 and 28 mg/dL, respectively. His total bilirubin was 3.3 mg/dL (direct = 0.5 mg/dL), serum SGOT 61 U/L (normal range = 3–38 U/L), SGPT 46 U/L (normal range = 3 to 35 U/L), and alkaline phosphatase 78 U/L (normal range = 38 to 126 U/L). No serum lactate dehydrogenase was ordered. Chest and abdominal X-rays were unremarkable. He was human immunodeficiency virus (HIV) antibody, rapid plasma reagin (RPR) test, and fluorescent treponemal antibody absorption test (FTA-ABS) positive. No group A streptococcus grew from the throat culture.

Following admission, he was given intravenous fluids and a single dose of methylprednisolone. His hematocrit and hemoglobin fell to 20% and 6.9 g. His total and direct bilirubin rose to 5.1 and 1.5 mg/dL, respectively. Eighteen hours after admission, he died.

At autopsy, the left flank contained a linear cluster of diagnonally oriented oval scars in a dermatome distribution. Petechiae covered the eyelids, palate, epiglottis larynx, and all serosal surfaces. The enlarged tonsils had fleshy red cut surfaces. The lungs (940 total) had dependent congestion. The pericardial cavity contained 100 mL of clear, dark yellow fluid. The 400-g heart was pale, with epicardial and myocardial petechiae. The liver and

pancreas were unremarkable. The 400-g spleen had prominent follicles. The renal surfaces were covered with petechiae. The adrenal glands were thinned and had multiple petechiae. Axillary, inguinal, cervical, celiac, periportal, and paraaortic lymph nodes were enlarged (up to 4 cm) with red, fleshy cut surfaces. The small bowel contained multiple, dark-red, firm, submucosal polypoid masses. The 1400-g brain was grossly normal.

Microscopically, the myocardium showed focal hemorrhagic necrosis with no inflammatory infiltrate. These areas contained arterioles filled with eosinophilic, granular thrombi. A hyperplastic layer of endothelial cells covered the thrombi, forming hillocks. The epicardial coronary arteries were normal. Kaposi's sarcoma was present in the gastrointestinal tract and lymph nodes. Thrombi occluded the neoplastic vessels of the sarcoma (Fig. 1). They were also present in the normal arterioles of lymph nodes, adrenal glands, and kidneys. The brain, pancreas, liver, spleen, and lungs lacked thrombi.

Results

Clinical Findings

The clinical features are summarized in Tables 1 and 2. The mean age of the cases was 37 years, and the age range was 24 to 51 years. Of the 8 patients, 4 were women. Our male:female ratio for natural autopsies is 2.2:1, so the female preponderance of our TTP cases may be greater than the unadjusted 1:1. Our black/white ratio for natural autopsies is 6:1, so the black preponderance is again greater than 1:1. No patient had recent or concurrent infections, and none of the women were pregnant. Only one patient was immunodeficient as a result of HIV. All the patients were apparently well before their final illness, except one who had rheumatoid arthritis and idiopathic epilepsy. He took sulindac, thioridazine, phenobarbital, phenytin, primidone, and cimetidine. The other patients took no medications. One patient (Case 8) had testicular cancer that had been successfully treated five years before his death.

The duration of symptoms was four days or less in six patients and seven to fourteen day in two others, as seen in Table 1. Three patients had no or slightly elevated (99.0°F

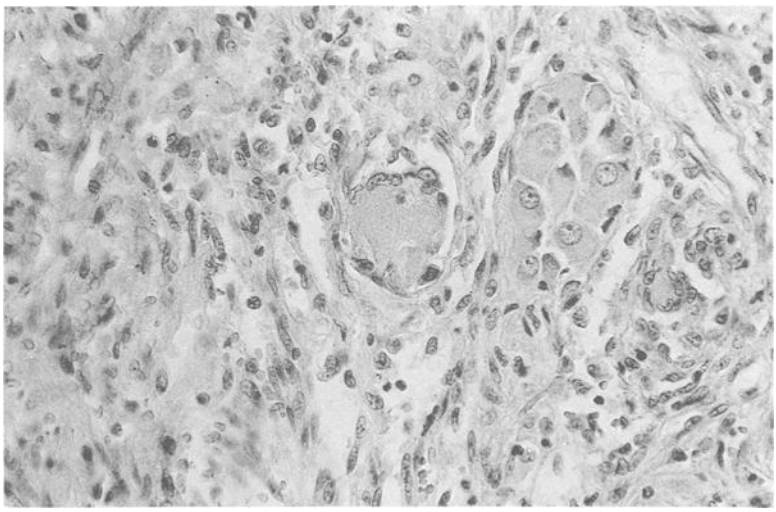

FIG. 1—*Thrombus within neoplastic vessel of Kaposi's Sarcoma (hematoxylin and eosin, original magnification ×310).*

TABLE 1—*Summary of clinical data.*

Case	Age	Sex	Race	Duration, days	Fever, °F[a]	Skin Petechiae
1	24	F	black	2	unknown	no
2	31	M	white	3	99	yes
3	42	F	black	7	100.4	no
4	42	F	black	4	101.8	no
5	37	M	white	2–3	unknown	yes
6	32	M	black	7–14	100.2	no
7	34	F	white	3	98.6	yes
8	51	M	white	2–3	none	no

[a]°C = (°F − 32) × 0.555.

TABLE 2—*Summary of symptoms.*

Symptoms	Number of Patients
Vomiting	3
Chest/abdominal pain	3
Fatigue/weakness	3
Dyspnea	1
Headache	2
Seizures	1
Arm numbness	2
Light-headness	1

[37.2°C]) temperatures. Three patients had fevers over 100.0°F (37.7°C), and two cases had no recorded temperatures. Petechiae were seen on three of the white patients and none on the black patients. Three patients had no neurologic symptoms, while three had mild or nonspecific findings such are lethargy, headache, and lightheadedness. One patient had seizures and arm numbness, while another had transient left-sided weakness and headache. Abdominal pain or vomiting or both was present in five of the eight patients. General fatigue was present in two patients. None of the patients received platelet transfusion and only Case 4 was transfused two units of packed red blood cells.

Laboratory Findings

Table 3 summarizes the laboratory results. One patient died before lab tests were drawn. The remaining patients were anemic, with the hematocrit varying from 21.6 to 29. Four cases had schistocytes, while three had moderate anisocytosis and poikilocytosis, as per laboratory records. Only one peripheral smear was available for this review. All patients were thrombocytopenic, varying from 8 to 41K platelet count. The white blood count varied from 4.7 to 14.3K. Prothrombin and partial thromboplastin times, when available, were all normal. The serum lactate dehydrogenase was done on only three patients, but was markedly elevated in all, 669, 1066, and 1720 U/L (normal = 45 to 90 U/L). Except in Cases 1, 7, and 8, the creatinine and blood urea nitrogen were normal. Urinalysis, when available, consistently revealed hematuria and proteinuria. Case 2 with AIDS was HIV, RPR, and FTA-ABS positive. Toxicology tests were negative in Cases 1 and 5. Toxicology in Case 8 showed small amounts of diazepam and nordiazepam in the blood, urine, liver, and gastric contents. Cases 5, 6, and 7 were HIV negative by enzyme-linked immunosorbent assay (ELISA).

TABLE 3—*Laboratory data summary.*

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
HGB, g	5.5	9	9.6	7	n/a[a]	7.8	10	9.4
HCT, %	18	26	29	21.6	n/a	22.4	29	28.5
PLATct, ×10	10	8	low	38	n/a	30	12	41
WBC, ×10	6	5.8	11.3	4.7	n/a	14.3	8.9	8.7
BL smear	[b]	[c]	[c]	[b]	n/a	[b]	[b]	[c]
PT, s	11.8	9.8	9.2	11.4	n/a	13	13.2	n/a
PTT, s	35	26	27	n/a	n/a	26	24	n/a
LDH, U/L	n/a	n/a	n/a	669	n/a	1720	n/a	1056
CRE, mg/dL	1.8	1.4	0.9	1.1	n/a	1.8	n/a	4.3
BUN, mg/dL	31	28	16	13	n/a	23	60	73
URIN MICRO	n/a	RBC 10–25/hpf	n/a	RBC 120–150/hpf	n/a	RBC 10–20/hpf	n/a	RBC 120–150/hpf
URIN PROT	n/a	protein 3+	n/a	yes, 3+	n/a	yes, 2+	n/a	yes, 3+

[a]n/a = not available.
[b]Schistocytes.
'Moderate anisocytosis and poikilocytosis.

Autopsy Findings

The autopsy findings are summarized in Table 4. Petechiae were present on the serosal surfaces, endocardium or pericardium (Fig. 2) in all cases. The adrenal glands had multiple small hemorrhagic foci (Fig. 3). Four patients had pulmonary edema, two had gastrointestinal hemorrhage, and one had cholecystitis and choledochocystitis. The patient with AIDS had Kaposi's sarcoma of the gastrointestinal tract and lymph nodes. The average heart, brain, spleen, and combined kidney and lung weights were 446, 1292, 311, 440, and 1190 g, respectively. (Microscopic sections were not available from all the organs summarized in Table 5; therefore, the results may total less than eight.)

Microthrombi were present in the precapillary arterioles of the heart in all eight cases. The conduction system was examined in Cases 1 and 5 only. In Case 1, both the sinoatrial (SA) and atrioventricular (AV) nodes contained microthrombi. In Case 5, only the SA node had microthrombi and hemorrhage. The AV node and His bundle were normal. Microthrombi were also numerous in the adrenal gland (six of six cases), lymph node (five of six cases), kidney (eight of eight cases), and pancreas (six of seven cases). They were present in the skin, when sampled (one of one case). In contrast, they were less frequently found in the brain (two of seven cases), lung (three of eight cases), spleen (three of eight cases), gastrointestinal tract (three of seven cases), liver (four of eight cases), bone marrow (three of seven cases), and thyroid (two of five cases). Microthrombi were also present in the gallbladder and common bile duct in Case 3 with cholecystitis and choledochocystitis. Of the five patients with neurologic symptoms, only two had microthrombi. Of the four patients with pulmonary edema, only two had accompanying microthrombi or hemorrhage. Of the two patients with gastrointestinal hemorrhage, none had microthrombi within the sampled sections.

Microscopically, the granular eosinophilic microthrombi did not usually occlude the arteriolar lumen completely, but were often covered by hyperplastic endothelium (Fig. 4). The dilated arterioles, combined with the endothelial-covered thrombi, stood out in such organs as the heart and adrenal gland (Fig. 5).

Discussion

Thrombotic thrombocytopenic purpura is characterized by microangiopathic hemolytic anemia, thrombocytopenic purpura, neurologic symptoms, renal disease, and fever [5].

TABLE 4—*Autopsy findings.*

Findings	No. of Cases
Petechiae	8
Effusion/ascites	4
Pulmonary edema	4
Gastrointestinal bleeding	2
Edematous kidneys	2
Coronary atherosclerosis (less than 50% narrowing)	2
Choledochocystitis	1
Pericarditis	1
Kaposi's sarcoma	1
Fatty liver, mild	2
Multiple hepatic hemangiomas	1
Pulmonary emphysema	1

FIG. 2—*Right ventricular endothelium contains extensive focal hemorrhage.*

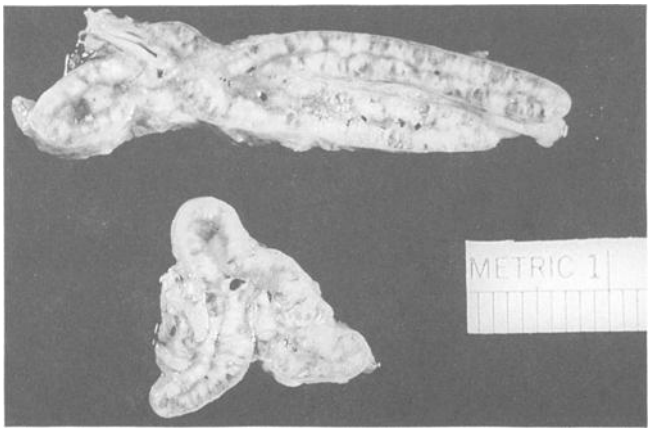

FIG. 3—*Transverse sections of both adrenal glands show the many foci of cortical hemorrhage.*

TABLE 5—*Microscopic findings, summary of the presence of thrombi.*

Site	Present	Absent	Not Available
Heart	8(100%)	...	...
Kidney	8(100%)	...	...
Adrenal	6(100%)	...	2
Skin	1(100%)	...	7
Pancreas	6(86%)	1(14%)	1
Lymph node	5(83%)	1(17%)	2
Liver	4(50%)	4(50%)	...
Bone marrow	3(43%)	4(57%)	1
Gastrointestinal tract	3(43%)	4(57%)	1
Thyroid	2(40%)	3(60%)	3
Lung	3(37%)	5(63%)	...
Spleen	3(37%)	5(63%)	...
Brain	2(28%)	5(72%)	1

The incidence of TTP varies from 1/48 000 hospital admissions [5] to 1/1100 hospital autopsies [6]. Our incidence is 1/2085 natural death autopsies or 1/23 000 deaths in Dade and Broward counties. Most cases occur between the first and fourth decades, with a peak incidence in the third decade [5,6]. Children are rarely affected [5,6]. Women are more often affected than men [6]. Our series, in addition, also shows a black predominance. Moschcowitz reported the first case in a 16-year-old girl who developed upper extremity weakness and pain, fever, and pallor. She died 5 days after admission, but never developed renal insufficiency [7]. This case reminds us that all features of the pentad are often not present in any single case. Ridolfi and Bell found that only 40% of their cases (104/258) had all 5 features, while 74% (192/258) had anemia, purpura, and neurologic symptoms [5]. All our patients had microangiopathic anemia and thrombocytopenia, but only 5 had neurologic symptoms and fewer had documented thrombi at autopsy. Although this may appear at odds with previous studies, one must remember

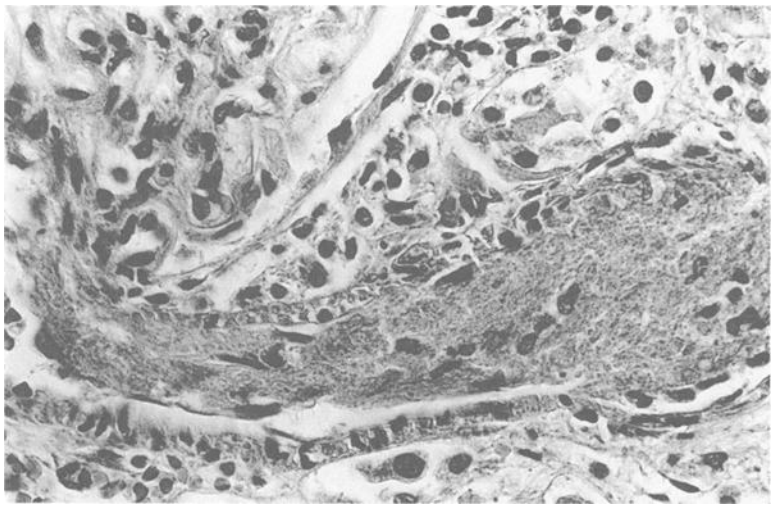

FIG. 4—*This granular thrombus nearly occludes afferent arteriole in kidney. Note the covering of hyperplastic endothelial cells (hematoxylin and eosin, original magnification ×500).*

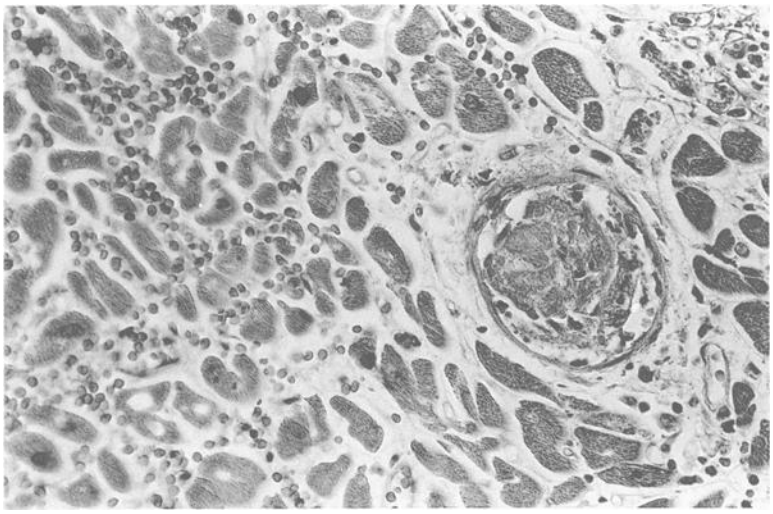

FIG. 5—*A thrombus fills this dilated arteriole in the heart. Note the prominent vessel and surrounding hemorrhage with no small leukocyte reaction (hematoxylin and eosin, original magnification ×310).*

that all the reported series are clinical and involve patients who lived long enough (and often recovered!) to be completely evaluated. Therefore, the patients in our series may not have all the features because they did not survive long enough to manifest them or be completely evaluated. Treatment with fresh frozen plasma or platelets (inadvertently) may also account for these differences. None of our patients received platelet transfusions, although one patient was given packed red blood cells. Only 3 of our patients were febrile. Fever is thought to be the result of ischemic damage to the hypothalamus [*8*]. This may explain the lower incidence of fever, since our patients had fewer neurologic sequelae.

The laboratory features help confirm the diagnosis. Microangiopathic anemia and thrombocytopenia are present in 98 and 83% of clinical cases [*5*]. The peripheral smear shows schistocytes or other misshapen red blood cells (in our three cases called moderate poikilocytosis). The degree of microangiopathic changes varies depending on the number of microthrombi and the efficiency of the spleen to clear the misshapened red cells [*9*]. The normal prothrombin and partial thromboplastin times (as in our cases) contrast with acute disseminated intravascular coagulation, in which they are prolonged. The serum lactate dehydrogenase (LDH) is often markedly elevated in cases of TTP [*9*]. Renal insufficiency, as defined by creatinine greater than 2.0 mg/dL or blood urea nitrogen (BUN) greater than 30 mg/dL, or both, is seen in 45% of clinical cases and three of our cases [*5*]. Hematuria and proteinuria is seen in 76 and 59% of clinical cases [*5*] and when a urinalysis was done, all of our cases. We mention the laboratory findings because most of our patients survived long enough to have an initial laboratory evaluation.

One should not infer from the discussion above that the diagnosis of TTP rests solely on the clinical and laboratory history. One can diagnose TTP confidently from the gross and microscopic examination. The gross features are not distinctive and consist of widespread petechiae and ecchymoses [*10,11*]. There is usually no macroscopic evidence of infection or infarction [*11*]. Microscopically, thrombi occlude capillaries and pre-capillary arterioles [*7,10–14*]. These thrombi consist of platelets in the early or initial lesions and later become organized.

Asada et al. demonstrated that the thrombi in TTP stained strongly for Factor VIII-related antigen and weakly for fibrinogen/fibrin using a peroxidase-antiperoxidase tech-

nique. Thrombi in acute disseminated intravascular coagulation showed the reverse staining [*15*]. Electron microscopy has shown that TTP thrombi are degranulated and altered platelets, while DIC thrombi consist of polymerized fibrin [*15*]. The thrombi of TTP are traditionally periodic acid Schiff positive [*14*] and phosphotungstic acid hematoxylin negative [*15*], but staining may vary with the age of the thrombi [*16*].

Associated with the thrombi is a prominent endothelial proliferation producing intravascular hillocks [*10,12*]. Although some authors state that veins are involved [*14*], Orbison and others have convincingly demonstrated that these are aneurysmally dilated arterioles rather than veins [*10,12*]. The kidney cortex (adjacent to the medulla), outermost adrenal cortex, myocardium, pancreas, and brain are commonly involved (at least in hospital autopsies). Lymph nodes, spleen, bone marrow, thyroid, gastrointestinal tract, and liver are less often involved. The lung is surprisingly spared in most cases [*10–13,15*].

This widespread distribution contrasts with hemolytic-uremic syndrome (which is morphologically identical to TTP) and may be missed if only a few organs are sampled. Thrombi in disseminated intravascular coagulation commonly involve the capillaries of the lung and renal glomeruli [*15*]. While present in other organs, they are not seen with the frequency and magnitude of TTP [*17*]. Despite the abundant thrombi found in TTP, few cells show any morphologic evidence of ischemic injury. The arteriole wall and surrounding parenchyma contain little or no inflammation. This is in striking contrast to small-vessel vasculitis (for example, Rickettsia infection). Stromal hemorrhage and edema surround the thrombosed vessels. Given the abundance and widespread distribution of the thrombi, as well as their distinctive morphologic features, one can accurately diagnose TTP at autopsy. All our cases shared this morphology, except for the brain, where thrombi were rarely demonstrated. Again, this may reflect the difference between early untreated TTP (our cases) and late TTP (most clinical studies) in which the patients have survived for a longer period of time and are treated (sometimes inadvertently with platelet transfusions).

If little or no ischemic injury is present despite the many thrombi, why do these people die suddenly? In the heart, ischemic injury does occur, albeit rarely, compared to the number of thrombi.

Ridolfi et al. systematically examined the conduction system and found thrombi and hemorrhage within the atrio ventricular node and His bundle, but not in the sinoatrial node or bundle branches [*18*]. They found these changes in seven of ten cases, and, although hemorrhage was present, no necrosis was seen in any case [*18*]. James and Monto discovered thrombi in the sinoatrial and atrio ventricular nodes, as well as, necrosis in the His bundle [*19*]. The extent of necrosis within the conduction system can be sparse and easily missed. James and Monto found the less than 1-mm area of necrosis in the His bundle only after sectioning the entire bundle serially at 6 μm [*19*].

Conduction system involvement manifests itself by various bradyarrhythmias, atrioventricular dissociation, and sudden death [*3,18,19*]. We examined the cardiac conduction system in two cases and found thrombi, with hemorrhage, but no necrosis. Both the sinotrial and atrioventricular nodes were involved. The epicardial coronary arteries lacked significant atherosclerosis and thrombi, in accord with other investigators [*3,18,19*]. Macroscopic infarction of the heart (as well as brain, kidney, and intestines) has been described in various case reports [*16,20,21*]. In one case, however, nonbacterial thrombotic endocarditis was present and could account for the infarction [*20*]. In other cases [*16,21*] TTP was clearly a questionable diagnosis. The extremely rare occurrence of macroscopic infarction in TTP should make one reconsider the diagnosis. Microvascular involvement of the heart and cardiac conduction system is the most common mechanism of sudden death in TTP.

Other mechanisms of rapid death exist in TTP, including injury to the lungs, gastrointestinal tract, and extrahepatic biliary system [*4,8,22,23*]. Thrombi are surprisingly rare

in the lung of TTP victims. This may be due to bradykinin stimulation of prostaglandin I2, a potent inhibitor of platelet aggregation [*15*]. Ridolfi et al. found thrombi in 5 of his 17 cases and only associated with focal intraalveolar hemorrhage [*18*]. Pulmonary edema and congestion producing heavy lungs was more common (9 of 17 cases) and attributed to one or a combination of the following factors: cardiac insufficiency as a result of microvascular injury and ischemia, severe anemia producing high cardiac output failure, renal failure, central nervous system involvement, or associated pneumonia [*8,22*]. Rarely, the lung pathology can overshadow the other organs producing fulminant respiratory failure and death [*22,24*]. Note that in one case, this occurred immediately after the woman received 55 units of platelets [*22*]. Intralveolar hemorrhage has also been reported in TTP as a mechanism of death [*24*]. TTP can also cause massive gastrointestinal bleeding and death [*4*]. TTP has been reported to cause pancreatitis, cholecystitis, and nonspecific abdominal pain [*5,6,23,25,26*]. These gastrointestinal problems are rarely fatal alone, and patients recover or die of other mechanisms. We had one fatal case of cholecystitis and choledochocystitis as a result of TTP.

We also describe one patient (Case 2) with both AIDS (Kaposi's sarcoma present) and TTP. He had no symptoms before his fatal illness. His Kaposi's sarcoma was confined to the gut and lymph nodes and diagnosed at autopsy. Interestingly, thrombi occluded the neoplastic vessels as well as the non-neoplastic arterioles and capillaries. Recently, multiple case reports (13 total) describe TTP in patients with HIV-I (human T lymphocyte virus-III [HTLV-III]) infection [*27–31*] and HTLV-I infection [*32*]. Only 2 of the 13 patients died and only 1 case briefly mentions the autopsy findings [*29*]. While some authors [*30,31*] postulate an association between TTP and HIV infection, the exponential rise in HIV-infected individuals who then coincidentally develop TTP more likely explains the apparent increase in concurrent TTP and HIV infection. As is the case of TTP patients who are appropriately treated, most (83%) of these patients survived the episode and were discharged.

Thrombotic thrombocytopenic purpura causes sudden death, but is often overlooked and misdiagnosed, as in two of our cases. Widespread petechiae in a previously healthy young person, in the absence of any other gross abnormalities, should prompt careful sampling of all organs, including the cardiac conduction system. The distinctive microscopic morphology should establish the diagnosis. Clinical history and any laboratory data will help to corroborate the diagnosis.

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