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Differentiating malignant hypertension-induced thrombotic microangiopathy from thrombotic thrombocytopenic purpura

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Abstract

Objectives: Malignant hypertension can cause thrombotic microangiopathy (TMA) and the overall presentation may mimic thrombotic thrombocytopenic purpura (TTP). This presents a dilemma of whether or not to initiate plasma exchange. The objective of the study was to determine the clinical and laboratory manifestations of malignant hypertension-induced TMA, and its outcomes.

Methods: Using several search terms, we reviewed English language articles on malignant hypertension-induced TMA, indexed in MEDLINE by 31 December 2013. We also report a new case. All these cases were analyzed using descriptive statistics.

Results: A total of 19 patients, with 10 males, had a median age of 38 years at diagnosis; 58% had a history of hypertension. Mean arterial pressure at presentation was 159 mmHg (range 123–190 mmHg). All had prominent renal dysfunction (mean creatinine of 5.2 mg/dl, range 1.7–13 mg/dl) but relatively modest thrombocytopenia (mean platelet count of 60×103/µl, range 12–131×10^3/µl). Reported cases ($n = 9$) mostly had preserved ADAMTS-13 activity (mean 64%, range 18–96%). Following blood pressure control, the majority had improvement in presenting symptoms (100%) and platelet counts (84%); however, only 58% had significant improvement in creatinine. More than half (53%) needed hemodialysis. One patient died of cardiac arrest during pacemaker insertion.

Conclusion: Prior history of hypertension, high mean arterial pressure, significant renal impairment but relatively modest thrombocytopenia and lack of severe ADAMTS-13 deficiency (activity <10%) at diagnosis are clues to diagnose malignant hypertension-induced TMA. Patients with malignant hypertension respond well to antihypertensive agents and have favorable nonrenal outcomes.

Keywords: ADAMTS-13 deficiency, malignant hypertension, plasma exchange, renal failure, thrombocytopenia, thrombotic microangiopathy, thrombotic thrombocytopenic purpura

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Introduction

The clinical definition of thrombotic thrombocytopenic purpura (TTP) is the presence of unexplained microangiopathic hemolytic anemia and thrombocytopenia with or without renal dysfunction, fever, neurological deficit or variable pattern of systemic tissue injury from microvascular thrombosis. TTP is a disorder of von Willebrand factor (VWF) proteolysis, caused by either a congenital deficiency or an autoimmune antibody-mediated destruction of ADAMTS-13. Documenting severe ADAMTS-13 deficiency (<10%) supports the diagnosis of TTP [Sarode *et al.* 2014]. However, measurement of ADAMTS-13 activity is neither required nor appropriate for deciding the requirement of plasma exchange in the initial management of a suspected case of TTP. It is clinically difficult to differentiate TTP from other causes of thrombotic microangiopathy (TMA) such as malignant hypertension. Current recommendations are to initiate plasma exchange while evaluating for any alternate cause [George, 2010].

Hypertensive urgencies may affect as many as 1% of all hypertensive patients [Aggarwal and Khan, 2006] and account for 3% of all emergency room visits, and a quarter of all medical emergencies [Zampaglione *et al.* 1996]. Given its high incidence, malignant hypertension, although uncommonly associated with TMA, is an important etiology. In malignant hypertension, the autoregulatory mechanism fails, resulting in damage to the vascular wall. Disruption of the vascular endothelium causes plasma constituents (including fibrinoid material) to enter the vascular wall and obliterate the vascular lumen [Strandgaard and Paulson, 1989]. In most patients with renal failure related to malignant hypertension, renal biopsy demonstrates an obliterative vasculopathy with fibrinoid necrosis as well as fibrin and platelet clots [Zhang *et al.* 2008]. This luminal narrowing is believed to fragment erythrocytes and consume platelets leading to TMA [Akimoto *et al.* 2011]. Although plasma exchange is lifesaving in TTP, it is not as efficacious in other types of TMA [George, 2010].

The rarity of malignant hypertension-induced TMA impairs our understanding of this condition, optimal management and outcomes. Inability to differentiate TTP from malignant hypertension-induced TMA presents a dilemma of whether or not to initiate plasma exchange. We report an illustrative case of malignant hypertension-induced TMA and review existing literature to fill this knowledge gap.

Materials and methods

Two authors (N.K. and S.D.) searched MEDLINE through PubMed on 31 December 2013 and reviewed English language articles (case reports, case series and original research articles) on malignant hypertension with features of TMA. The search was conducted using the following MeSH terms: 'Malignant Hypertension' AND 'Thrombotic microangiopathy', OR 'Malignant Hypertension' AND 'Thrombotic Thrombocytopenic Purpura', OR 'Severe Hypertension' AND 'Thrombotic Microangiopathy,' OR 'Hypertension' AND 'Microangiopathic Hemolytic Anemia.' All references were also checked for additional reports. All reports of TMA from malignant hypertension (idiopathic or secondary hypertension) in adults (18 years or older) were included. All case reports/series with adequate patient level data (case series which presented only summary data and not detail information about individual cases were excluded from analysis but reviewed in the discussion section) were analyzed using descriptive statistics to determine the clinical and laboratory manifestations, management and outcomes of malignant hypertension-induced TMA. Other relevant reports but without patient level data are reviewed in the Discussion. Including the case reported here, our review included 19 patients with malignant hypertension and the manifestations of TMA.

Results

Case presentation

A 33-year-old man presented with a 2 week history of abdominal and bilateral leg swelling, a 1 week history of intermittent occipital headaches and a 2-day history of blurry vision. The patient was not oliguric. Past medical history was significant for untreated hypertension and diabetes. Home medications included glargine and lispro insulin. He had a 10-pack-year smoking history and reported marijuana use once or twice a week. On examination, he had a blood pressure of 198/124 mmHg, heart rate of 82/min, oral temperature of 36.5°C and respiratory rate of 20/min. He had mild abdominal distention and bilateral leg swelling. The remainder of the physical examination including neurological and vision assessment at bedside was unremarkable. Laboratory tests revealed hemoglobin of 6.3 g/dl, platelet count of 77,000/μl, white blood count of 6300/μl, reticulocyte count of 10.2%, blood urea nitrogen of 29 mg/dl, creatinine of 2.45 mg/dl, lactate dehydrogenase (LDH) of 700 units/l (normal 98–192 U/l), haptoglobin <15 mg/dl and normal coagulation profile. Peripheral smear showed multiple schistocytes. Urine toxicology was positive for cannabinoids.

A possibility of malignant hypertension was considered, but classical TTP could not be ruled out. In addition to starting a labetalol drip, ADAMTS-13 activity level was ordered and then plasma exchange was started. With control of blood pressure, the platelet count and LDH started normalizing. Hence, plasma exchange was discontinued after 2 days. Subsequently, ADAMTS-13 activity was reported to be 70%, refuting the diagnosis of classical TTP. The patient was discharged home on oral antihypertensive agents and remained stable for 4 weeks after the discharge without any evidence of microangiopathic hemolysis or thrombocytopenia.

We describe a case of malignant hypertension-induced TMA where the patient improved clinically and his laboratory values normalized after control of blood pressure. This case illustrates that malignant hypertension is an important differential diagnosis of TMA, particularly in patients with significant hypertension.

Review of reported cases

Of 19 patients, 10 were male, with a median age of 38 years at diagnosis (Table 1) [Ekberg *et al.* 1974; Egan *et al.* 2004; Shibagaki and Fujika, 2005; Garewal *et al.* 2007; Hunt *et al.* 2007; Desai *et al.* 2008; Boctor and Pritchard, 2009; Li *et al.* 2009; Patel *et al.* 2009; Shavit *et al.* 2010; Bawany *et al.* 2011; Deguchi *et al.* 2012; Schauseil *et al.* 2012; Wu *et al.* 2013]. The history of hypertension was known in 58%. All the patients had elevated blood pressure at diagnosis, with a mean arterial pressure of 159 mmHg on average (range 123–190 mmHg). The most common presenting symptoms were neurological symptoms such as headache (58%), blurry vision (42%) or dizziness (21%); or gastrointestinal symptoms such as nausea/vomiting (42%), or abdominal pain (21%). None of the patients had fever. In addition to significant hemolytic anemia with schistocytes (mean hemoglobin of 8.8 g/dl, range 3.8–12.6 g/dl) and elevated LDH (mean of 1310 IU/l, range 135–4000 IU/l), all the patients had prominent renal dysfunction (mean creatinine of 5.2 mg/dl, range 1.7–13 mg/dl). The presence of oliguria was not reported in any of the cases. However, thrombocytopenia was relatively modest (mean platelet count of $60 \times 103/\mu l$, range $12–131 \times 103/\mu l$). Reported cases ($n = 9$) mostly had preserved ADAMTS-13 activity level (mean 64%, range 18–96%).

All the patients received antihypertensive treatment while nearly one third (32%) also received plasma exchange. Of the cases that reported the particular antihypertensive agent used ($n = 12$), three-quarters (75%) started with intravenous agents while a quarter (25%) used oral agents alone. Following the control of blood pressure, the majority had a significant improvement in presenting symptoms (100%) and platelet counts (84%); however, only 58% of the patients had significant improvement in renal function. More than half of the patients (53%) needed hemodialysis. At discharge or follow up ($n = 10$), the mean platelet count was $216 \times 103/\mu l$ (range $110–350 \times 103/\mu l$) and the mean creatinine level was 3.9 mg/dl (range 1.1–11.3 mg/dl). One patient died of cardiac arrest during pacemaker insertion.

Discussion

Malignant hypertension is an important cause of TMA. Published series have shown an incidence of TMA in 20–40% of patients with malignant hypertension [Kadiri and Olutade, 1991; van den Born *et al.* 2005; Akimoto *et al.* 2011]. In the Oklahoma TTP registry, malignant hypertension ($n = 6$) was determined to be the underlying cause of TMA referred for plasma exchange in about 2% of cases [George, 2010]. Despite these figures, our review showed only 18 reported cases with detailed information. Thus, malignant hypertension-induced TMA is likely to be unrecognized and under-reported. However, differentiating TTP and malignant hypertension-induced TMA is meaningful from both therapeutic and prognostic standpoints. Many experts believe that plasma exchange should be considered in TTP after the exclusion of alternate causes such severe malignant hypertension, implying that the presence of a severe malignant hypertension excludes TTP [Schwartz *et al.* 2013]. However, TTP literature does not provide explicit information about the extent of hypertension noted in TTP patients. Importantly, one-third of reported cases of malignant hypertension-induced TMA have undergone plasma exchange, thus highlighting the clinical dilemma in reliably differentiating the two conditions and foregoing plasma exchange based on initial clinical suspicion.

Our review presents several important similarities and differences between malignant hypertension-induced TMA and TTP. Both TTP and malignant hypertension-induced TMA mostly present with neurological and gastrointestinal symptoms. In malignant hypertension-induced TMA, however, patients do not have fever. Prior history of hypertension and higher mean arterial pressure at presentation are possible clues to a diagnosis of malignant hypertension. The greater degree of renal impairment at diagnosis, relatively modest thrombocytopenia and lack of severe ADAMTS-13 deficiency (activity $<10\%$) can further differentiate malignant hypertension from TTP.

Prior publications are consistent with our findings (Table 2). Van den Born and colleagues demonstrated a higher serum creatinine level and urinary protein excretion at admission among

Table 1. Summary of the reported cases of malignant hypertension-induced thrombotic microangiopathy.

Parameter at presentation	Value, *n* (%)
Age, median (years)	38
Male/Female	10/9
Pre-existing hypertension	11 (58)
MAP (mmHg)	160*
Hemoglobin (g/dl)	8.8*
Platelet ($\times 10^3$/μl)	59*
LDH (IU/l)	1118*
Creatinine (mg/dl)	4.14*
ADAMTS-13 activity (%)	68*
Anti-hypertensive agent use	19 (100)
Plasma exchange	6 (32)
Hemodialysis	10 (53)
Symptomatic improvement$	19 (100)
Improvement in thrombocytopenia$	16 (84)
Improvement in renal function$	11 (58)
Platelet at last follow up ($\times 10^3$/μl)	190.5*
Creatinine at last follow up (mg/dl)	2.55*

*Median.
$Improvement after the control of hypertension.
LDH, lactate dehydrogenase; MAP mean arterial pressure.

malignant hypertension patients with *versus* without microangiopathic hemolyic anemia [van den Born *et al.* 2005]. Akimoto and colleagues showed a higher serum creatinine, lower hemoglobin and lower platelet count among malignant hypertension patients with *versus* without TMA; however, the difference was not statistically significant likely because of small number of patients [Akimoto *et al.* 2011]. These prior publications, based on institutional experiences, focus on the comparison of patients with malignant hypertension with *versus* without microangiopathy, rather than with TTP. The use of plasma exchange and ADAMTS-13 level are not extensively discussed.

Our study, which collects previously reported experiences from different centers, aims to compare malignant hypertension-induced TMA to TTP with a goal to help distinguish between the two conditions at diagnosis. Compared with TTP, cases with malignant hypertension-induced TMA are shown to have higher blood pressure at presentation, signs of hypertensive heart disease [van den Born *et al.* 2005] or retinopathy, higher platelet count [Shibagaki and Fujita, 2005; Shavit *et al.*

Table 2. Comparison of different series of malignant hypertension-induced thrombotic microangiopathy and patients in the Oklahoma Thrombotic Thrombocytopenic Purpura Registry with ADAMTS-13 ⩾10%.

Parameter at presentation	Our review (*n* = 19)	Van den Born [van den Born *et al.* 2005] (*n* = 26)	Akimoto and colleagues [Akimoto *et al.* 2011] (*n* = 7)	Oklahoma TTP Registry [George, 2010] (*n* = 56)
Age, mean (years)	39	41	39	2–85
Sex (% women)	47	54	28	66
Preexisting hypertension (%)	11 (58)	12 (46)	6 (86)	–
Mean SBP (mmHg)	218	242	252	–
Mean DBP(mmHg)	129	150	160	–
Hemoglobin (g/dl)	8.8	6.5*	9.3	HCT of 27*
Platelet ($\times 10^3$/μl)	60	90*	81	43*
LDH (IU/l)	1310	786*	1123	989*
Creatinine (mg/dl)	5.2	7.8*	8.3	3.3*
Outcomes				
Need for hemodialysis (%)	10 (53)	15 (58)	4 (57)	(43)
CKD requiring long-term renal replacement therapy (%)	6 (32)	9 (35)	2 (29)	–
Death (%)	1 (5)	2 (8)	0	(21)

* These values are median; other values are mean.
CKD, chronic kidney disease; DBP, diastolic blood pressure; HCT, hematocrit; IU, international unit; LDH, lactate dehydrogenase; SBP systolic blood pressure; TTP, thrombotic thrombocytopenic purpura.

2010] and higher ADAMTS-13 activity [van den Born *et al.* 2008]. Patients with malignant hypertension, compared with healthy controls, can have lower levels of ADAMTS-13; the levels negatively correlated with LDH levels, platelet count and the presence of schistocytes. However, the deficiency of ADAMTS-13 is always mild (activity >50%) [van den Born *et al.* 2008]. In the Oklahoma TTP Registry, none of the patients with malignant hypertension-induced TMA had ADAMTS-13 activity <10% [George, 2010].

We also demonstrated that, unlike TTP, patients with malignant hypertension respond well to antihypertensive agents, do not require plasma exchange and have favorable nonrenal outcomes; however, patients frequently end up with persistent renal failure. Aggressive management of blood pressure in malignant hypertension-induced TMA has been previously shown to result in resolution of TMA and gradual return of renal function [Zhang *et al.* 2008]. Although high creatinine levels and systolic hypertension at presentation are associated with a lower chance of renal recovery [van den Born *et al.* 2005], malignant hypertension patients ultimately may have more favorable nonrenal prognosis than other thrombotic microangiopathies [Zhang *et al.* 2008].

Conclusion

In conclusion, prior history of hypertension, high mean arterial pressure, significant renal impairment but relatively modest thrombocytopenia and lack of severe ADAMTS-13 deficiency (activity <10%) at diagnosis are clues to diagnose malignant hypertension-induced TMA. Future studies should focus on validating these observations, and could lead to formulation of a model to differentiate TTP and malignant hypertension-induced TMA. Given the rarity of TTP and other TMA, this may be possible only through a prospective multicenter registry.

Authors' note

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Conflict of interest statement

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