Mod Rheumatol (2008) 18:403–406
DOI 10.1007/s10165-008-0061-0

CASE REPORT

Thrombotic thrombocytopenic purpura–hemolytic uremic syndrome and adult onset Still's disease: case report and review of the literature

Mehmet Sayarlioglu · Hayriye Sayarlioglu · Mesut Ozkaya · Ozan Balakan · Mehmet Ali Ucar

Received: 8 November 2007 / Accepted: 20 February 2008 / Published online: 22 April 2008

Abstract Thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP/HUS) is a multisystem disorder characterized by consumptive thrombocytopenia, microangiopathic hemolytic anemia, neurologic symptoms, renal function abnormalities, and fever. Coexistence of TTP/HUS and adult onset Still's disease (ASD) is extremely rare. We report the case of a 46-year-old woman who presented with fever, arthritis, myalgias, petechia on skin and confusion five years after the onset of ASD. Thrombocytopenia, renal failure, marked elevation lactate dehydrogenase, and red cell fragmentation on peripheral blood smear were observed. We made a diagnosis of TTP/HUS associated with ASD, according to physical examination and characteristic laboratory data. She recovered from the TTP/HUS following daily sessions of therapeutic plasma exchange with fresh frozen plasma replacement and glucocorticoid therapy. Awareness of the possible development of TTP/HUS in ASD is important for early diagnosis and treatment.

M. Sayarlioglu (✉)
Department of Internal Medicine,
Division of Rheumatology,
Sutcu Imam University Medical Faculty,
Kahramanmaras, Turkey
e-mail: sayarli@hotmail.com

H. Sayarlioglu
Department of Internal Medicine,
Division of Nephrology,
Sutcu Imam University Medical Faculty,
Kahramanmaras, Turkey

M. Ozkaya · O. Balakan · M. A. Ucar
Department of Internal Medicine,
Sutcu Imam University Medical Faculty,
Kahramanmaras, Turkey

Keywords Hemolytic uremic syndrome · Plasmapheresis · Still's disease · Thrombotic thrombocytopenic purpura

Introduction

Adult onset Still's disease (ASD) is a systemic disorder that is typically characterized by spiking high fever, arthritis, evanescent maculopapular rash, myalgia, serositis, leukocytosis and the involvement of various organs. There are no hallmark clinical or pathological findings, and so the diagnosis of ASD is based on clinical findings as well as the exclusion of infections, malignancy, and other febrile polyarthritis [1].

We present a patient diagnosed with adult Still's disease who developed thrombocytopenic thrombocytic purpura and/or hemolytic uremic syndrome (TTP/HUS). Coexistence of TTP/HUS and ASD is extremely rare. We report the eleventh published case of TTP/HUS associated with Still's disease.

Case presentation

A 46-year-old woman with a five-year history of ASD was admitted to our hospital because of fever, arthralgias, myalgias, petechia on skin, general malaise, and confusion. She was diagnosed with high spiking fever accompanied by an evanescent rash, sore throat, malaise, myalgias, neutrophilic leukocytosis, and bilateral inflammation of the carpometacarpal joints, wrists, and ankles five years ago. Since her onset of ASD, the patient had eight or ten exacerbations of spiking fever, evanescent rash and polyarthritis at another hospital. Prednisolone, methotrexate

and sulfasalazine were used. At the time of this current admission, physical examination revealed a blood pressure of 110/70 mmHg, a temperature of 40.5 °C, tachycardia, petechia on skin, active arthritis on bilateral hand joints and knee joints, yellow sclera and periorbital edema. Paralysis and pathologic reflex were not observed.

Laboratory evaluation revealed: Hct 33%, Hb 11.6 g/dl, white blood cell count (WBC) of 4.1 × 10^9/l platelets 31 × 10^9/l, CRP 56 mg/l and erythrocyte sedimentation rate 98 mm/h. Prothrombin and activated partial thromboplastin times (PT, aPTT) and fibrinogen were normal. Biochemical values were: LDH 1551 U/l, albumin 3.3 g/dl, BUN 35 mg/dl, creatinine 1.9 mg/dl (after one day 2.5 mg/dl), AST 273 U/l, ALT 55 U/l, indirect bilirubin 2.3 mg/dl, direct bilirubin 0.4 mg/dl and electrolytes were within normal range. Serum ferritin level was markedly elevated (38.080 ng/dl). Coombs test was negative, and red cell fragmentation was observed on peripheral blood smear (Fig. 1). Urinalysis revealed 10–15 red cells, 10–15 leukocytes per high-power field, and proteinuria was absent. Thoracic radiography, electrocardiogram and echocardiography were also normal. Blood, urine, and stool cultures were negative. Serological evaluation for hepatitis B and C were negative. Laboratory evaluation for infection, systemic or malignant disease were negative: antinuclear antigen, antidsDNA, antiRNP, antiSM, antiJo1, anticardiolipine, c- and p-ANCA, cryoglobulins, rheumatoid factor, and tumor markers and complement levels were normal. Renal morphology appeared normal on ultrasonography.

She was treated empirically with intravenous corticosteroids and antibiotics for suspected sepsis, disseminated intravascular coagulation, or autoimmune disease. The association of microangiopathic hemolytic anemia, thrombocytopenia and renal failure led us to the clinical diagnosis of TTP/HUS associated with active ASD. The patient was treated with daily exchange plasmapheresis and 2 mg/kg prednisolone. After multiple plasma exchanges, the platelet count reached 150 × 10^9/l, and renal function returned to normal. The patient's symptoms began to improve: her fever resolved, her ferritin level decreased from 38,080 to 1,500 ng/l, and her LDH level decreased from 1,551 to 396 U/L. She was discharged in good condition. At five months after presentation, there has been no relapse and the patient continues to have normal renal function on low-dose prednisolone and methotrexate.

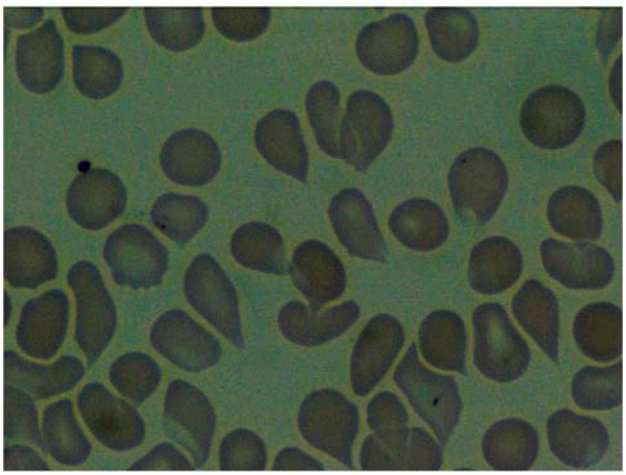

Fig. 1 Schistocytes on peripheral smear

Discussion

Thrombotic thrombocytopenic purpura–hemolytic uremic syndrome is a rare disorder of the blood coagulation system. TTP/HUS is classically the pentad of thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, renal dysfunction, and fever. TTP/HUS is associated with an ever-growing list of bacterial and viral infections, inflammatory and immunologic disorders, neoplasm, transplantation, pregnancy, and drugs (mainly chemotherapy agents). Endothelial damage may be the primary event in the pathogenesis of TTP/HUS, triggering a cascade of events that results in thrombotic microangiopathy [2]. These etiologies have been reasonably excluded, and none of the drugs usually associated with TTP/HUS were administered to this patient. The hallmark laboratory finding crucial to the diagnosis of TTP/HUS in this case is microangiopathic hemolytic anemia. The association of microangiopathic hemolytic anemia, thrombocytopenia and renal failure led us to the clinical diagnosis of TTP/HUS associated with ASD.

Distinguishing between TTP/HUS and disseminated intravascular coagulation (DIC) may be a somewhat more difficult task, and one that is based upon the history and laboratory studies. DIC is associated with different disorders from TTP/HUS, such as sepsis, shock, or an obstetrical complication including preeclampsia. DIC is a syndrome characterized by increased PT and aPTT, decreased platelet count, and decreased levels of fibrinogen [3]. In this case the levels of fibrinogen, PT and PTT in tests were normal.

If untreated, TTP/HUS in adults typically follows a progressive course in which irreversible renal failure and death are common outcomes [2, 4]. Plasma exchange reverses the platelet consumption that is responsible for the thrombus formation and symptoms that are characteristic of disorder. Plasma exchange is initially performed daily until the platelet count has normalized and hemolysis has largely ceased, as evidenced by a normal serum LDH concentration [5, 6].

A major breakthrough in our understanding of the pathogenesis of TTP/HUS is the discovery of deficient activity

Table 1 Main characteristics of patients with TTP/HUS and adult onset Still's disease

	Masson et al. [9]	Boki et al. [10]		Portoles et al. [11]	Diamond [12]	Domingues et al. [13]	Perez and Rodwig [14]	Hirata et al. [15]	Quéméneur et al. [16]	Okwuosa et al. [17]	This case
Sex	F	F	F	M	M	F	F	F	M	M	F
Age (years)	45	33	28	31	22	15	45	23	42	27	46
Time from ASD to TTP/HUS	17 years	3 years	NA	19 days	4 months	2 months	3 days	4 years	2 weeks	4 weeks	5 years
Fever	+	+	+	+	+	+	+	+	+	+	+
Arthralgia and/or arthritis	+	+	+	+	+	+	+	+	+	+	+
Sore throat	+	NA	NA	+	NA	NA	+	NA	+	+	+
Adenopathies	–	NA	–	–	NA	–	NA	NA	–	–	+
Rash	+	+	+	+	+	+	+	NA	+	+	+
Polynucleosis	+	NA	NA	+	NA	+	+	NA	+	+	+
Hyper-transaminasemia	–	NA	NA	+	NA	–	–	–	+	+	+
Anticardiolipin antibodies	NA	–	–	–	NA	NA	–	NA	+	–	–
Creatininemia (μmol/l)	660	123	187	565	942	502	HD	97	865	132	220
Diminished ADAMTS-13 activity	ND	NA	NA	ND	ND	ND	ND	+	ND	ND	ND
Kidney biopsy	Renal TMA (postmortem)	ND	ND	Arteriolar and glomerular TMA	Arteriolar and glomerular TMA	Arteriolar and glomerular TMA	ND	ND	Arteriolar and glomerular TMA	–	ND
Treatment	CS	PP, PI, CS, aspirin	PI, CS	PP, PI, aspirin, HD	PP, CS, IV Ig	CS, aspirin	CS, PP, HD, splenectomy, AZA	CS, ASA, PP	CS, IV Ig	PP, CS, Cy, vincristine	PP, CS
Outcome	Death	CR	CR	PR visual impairment	CR creatininemia 88 μol/l	Death	CR	CR	ESRD	PR visual impairment	CR

NA not available, *ND* not done, *TMA* thrombotic microangiopathy, *HUS* hemolytic-uremic syndrome, *ASD* adult onset Still's disease, *HD* hemodialysis, *CS* corticosteroids, *PP* plasmapheresis, *PI* plasma infusion, *IV Ig* intravenous immunoglobulins, *AZA* azathioprine, *Cy* cyclophosphamide, *CR* complete remissions, *PR* partial remissions, *ESRD* end stage renal disease

of the von Willebrand factor-cleaving protease, a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS)-13 [7, 8]. Severe ADAMTS-13 deficiency is an important pathogenetic factor for many cases of classical TTP. In the presence of ADAMTS-13 inhibitors, such as antibodies against ADAMTS-13, intravascular platelet thrombi develop and present as a clinical feature of TTP. In this case, these parameters were not studied because of technical insufficiency.

This case is the eleventh report in the literature on TTP/HUS with ASD (Table 1) [9–17]. In Table 1, the main characteristics of patients with TTP/HUS and ASD are summarized. The mean age is 32.45 ± 10.7 (15–46) years, female/male ratio is 7/4, and range of time from ASD to TTP/HUS is 3 days–17 years.

Among these eleven patients, five had TTP/HUS with severe renal failure. In these five patients, the diagnosis of renal thrombotic microangiopathy was proven histologically [9, 11–13, 16]. Two of the cases reported had a fatal outcome [9, 13].

The outcome mainly depends on the early application of treatment. Plasmapheresis, plasma infusion, corticosteroids and hemodialysis are the more extended treatments. Other measures, such as the use of aspirin, heparin, vincristine, intravenous immunoglobulins, cyclophosphamide, other immunosuppressive agents and splenectomy have not resulted in better outcomes in a controlled trial [2, 5, 6]. Our patient was successfully treated with plasma exchanges and high-dose corticosteroid therapy.

In summary, TTP/HUS has only rarely been reported in association with ASD. Awareness of the possible development of TTP/HUS in ASD is important for early diagnosis and treatment. Further studies into the pathophysiology of ASD will provide more information about the formation and modulation of platelet thrombi observed in TTP/HUS.

Conflict of interest There is no conflict of interest of this manuscript.

References

1. Cush JJ, Medsger TA Jr, Christy WC, Herbert DC, Cooperstein LA. Adult-onset Still's disease: clinical course and outcome. Arthritis Rheum. 1987;30:186–94.
2. Ruggenenti P, Noris M, Remuzzi G. Thrombotic microangiopathy, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura. Kidney Int. 2001;60:831–46.
3. Marder VJ, Martin SE, francis CW, Colman RW. Consumptive thrombo-hemorrhagic disorders. In: Colman RW, Hirsh J, Marder VJ, Salzman EW (eds) Hemostasis and thrombosis: basic principles and clinical practice, 2nd edn. 1987; Lippincott, Philadelphia, pp 975–1015.
4. Remuzzi G. HUS, TTP: variable expression of a single entity. Kidney Int. 1987;32:292–308.
5. George JN. Clinical practice. Thrombotic thrombocytopenic purpura. N Engl J Med. 2006;354:1927–35.
6. Moake JL. Thrombotic microangiopathies. N Eng J Med. 2002;347:589.
7. Furlan M, Robles R, Galbusera M, Remuzzi G, Kyrle PA et al. Von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. N Engl J Med. 1998;339:1578–84.
8. Levy GG, Nichols WC, Lian EC, Foroud T, McClintick JN et al. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. Nature. 2001;413:475–6.
9. Masson C, Myhal D, Menard H, Lussier A. Purpura thrombotique thrombopenique fatal chez une patiente atteinte dune maladie de Still de I'adulte. Rev Rhum Mal Osteoartric. 1986;53:389–91.
10. Boki KA, Tsirantonaki MJ, Markakis K, Moutsopoulos HM. Thrombotic thrombocytopenic purpura in adult Still's disease. J Rheumatol. 1996;23:385–7.
11. Portoles J, de Tomas E, Espinosa A, Gallego E, Nieva GS, Blanco J. Thrombotic thrombocytopenic purpura and acute renal failure in adult Still's disease. Nephrol Dial Transplant. 1997;12:1471–3.
12. Diamond JR. Hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP) complicating adult Still's disease: remission induced with intravenous immunoglobulin G. J Nephrol. 1997;10:253–7.
13. Domingues RB, da Gama AM, Caser EB, Musso C, Santos MC. Disseminated cerebral thrombotic microangiopathy in a patient with adult's still disease. Arq Neuropsiquiatr. 2003;61:259–61.
14. Perez MG, Rodwig FR Jr. Chronic relapsing thrombotic thrombocytopenic purpura in adult onset Still's disease. South Med J. 2003;96:46–9.
15. Hirata S, Okamoto H, Ohta S, Kobashigawa T, Uesato M et al. Deficient activity of von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura in the setting of adult-onset Still's disease. Rheumatology (Oxford). 2006;45:1046–7.
16. Quéméneur T, Noel LH, Kyndt X, Droz D, Fleury D et al. Thrombotic microangiopathy in adult Still's disease. Scand J Rheumatol. 2005;34:399–403.
17. Okwuosa TM, Lee EW, Starosta M, Chohan S, Volkov S et al. Purtscher-like retinopathy in a patient with adult-onset Still's disease and concurrent thrombotic thrombocytopenic purpura. Arthritis Rheum. 2007;57:182–5.