Acute Promyelocytic Leukemia Presenting as Ischemic Stroke in Young

Rajan Kapoor · H. P. Pati · Sanjeev Kumar Gupta · Nitin Gupta

Received: 25 July 2011 / Accepted: 14 January 2012 / Published online: 1 February 2012
© Indian Society of Haematology & Transfusion Medicine 2012

Abstract Coagulopathy in acute promyelocytic leukemia (APL) is a very complex disorder and is believed to result from interplay of various factors. Usually patients present with bleeding tendencies which can be life threatening. However, a few present with thromboses. Here, we report a young male with APL who presented with ischemic stroke in young.

Case Report

A 23-year-old male presented to casualty with 1 month history of fever, symptomatic anemia followed, around 15 days later, by bleeding tendencies in the form of epistaxis, hematemesis, and melena. Two days prior to presentation to the hospital, he developed slurring of speech, pooling of secretions in mouth, and facial deviation toward the left side. His prior medical history was unremarkable with no history of hypertension, diabetes, smoking or alcohol consumption. On examination he was drowsy but arousable, disoriented to time, place, and person. He had pallor with widespread petechiae. His BP was 128/86 mmHg with temperature of 38.3°C. He was uncooperative for detailed neurological assessment; however, he had evidence of facial paresis on left side with extensor plantar on the left side. Spleen was palpable 4 cm below left costal margin. On investigation, hemoglobin (Hb) was 75 gm/l, total leukocyte count (TLC)

was $85 \times 10^9/l$, and platelets were $45 \times 10^9/l$. Peripheral smear showed more than 90% abnormal hypergranular promyelocytes (Fig. 1). Blood chemistry was essentially normal. Coagulation profile revealed deranged prothrombin time (18 s with control of 12 s) with normal activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen levels. D-Dimer levels were raised. Urgent non-contrast CT scan of the head was carried out which showed a hypodense area suggestive of infarct in the right parieto-occipital region along with cerebral edema (Fig. 2). ECG showed sinus tachycardia with T wave inversion in anterior and lateral leads. Troponin (T) was negative. On the basis of peripheral smear findings and clinical presentation, the patient was immediately started on all-trans-retinoic acid (ATRA) at a dose of 45 mg/m². As he presented in Sanz high risk category with very high TLC, ATRA was followed by parenteral daunorubicin at dose of 60 mg/m². Blood component support with fresh frozen plasma, platelet concentrates, and packed RBC was given along with mannitol as the cerebral decongestant. Bone marrow examination done subsequently showed replacement by abnormal hypergranular promyelocytes with strong cytochemical positivity for myeloperoxidase (MPO) and sudan black (SBB) stains compatible with diagnosis of acute promyelocytic leukemia (APL) (Fig. 2). Immunophenotyping revealed positivity for CD 13, CD 33, CD 34, anti-MPO and negativity for HLA-DR, CD 2, CD 7, CD 79a, CD 117, and CD 19 in these cells. Co-expression of CD 10 was also noted. The diagnosis of APL was confirmed by positivity for PML-RAR α (promyelocytic leukemia-retinoic acid receptor alpha) fusion transcript by reverse-transcription-polymerase chain reaction (RT-PCR). However, his condition continued to deteriorate. A repeat CT scan performed on day 3 revealed significant increase in infarct size. The patient lapsed into deep coma and finally expired on 4th day.

R. Kapoor (✉) · H. P. Pati · S. K. Gupta · N. Gupta
Department of Hematology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India
e-mail: majrkapoor@gmail.com

Fig. 1 Bone marrow smear showing hypergranular promyelocytes, few with bilobed nuclei and occasional Auer rod (*arrow*) (Jenner Giemsa $\times 1,000$)

Fig. 2 Non-contrast CT scan head showing infarct in right temporo-parietal region

Table 1 Literature summary of thrombosis in acute promyelocytic leukemia (APL) patients

Patients (n)	Age (years)	WBC count ($\times 10^9/l$)	Thrombosed organ	Fatal	Reference number
1	29	14.5	DVT, PE	–	[5]
11	60 median age	17 median WBC count	DVT, sub endocardic ischemic disease	–	[7]
1	14	23.4	Budd-Chiari	Yes	[10]
3	32 median age	4.8 median WBC count	Liver, lung, kidney, spleen, MI	Yes	[11]
1	43	1.1	Kidney	–	[12]
1	49	1.0	Kidney $\pm$ heart	Yes	[13]
4	42.5 median age	<50	Widespread	Yes (all 4)	[14]
2	34.5 median age	33.2 median WBC count	Portal vein, kidney	–	[15]
1	32	NR	DVT brachiocephalic, popliteal	–	[16]
1	32	4.3	Budd-Chiari (hepatic vein)	–	[17]
4	>60	NR	MI	2 of 4	[18]
1	41 median age	45.7 median WBC count	Heart (RV)	–	[19]
1	20	45	Spleen, DVT, PE	–	[20]

WBC white blood cell, DVT deep vein thrombosis, PE pulmonary embolism, NR not recorded, MI myocardial infarction, RV right ventricle

Discussion

Acute promyelocytic leukemia is a subtype of acute myelogenous leukemia characterized by characteristic abnormal hypergranular promyelocytes in peripheral blood and bone marrow [1]. It typically presents with life threatening hemorrhagic diathesis which worsens with cytotoxic chemotherapy. Coagulopathy in APL is a very complex disorder

and is believed to result from interplay of three main factors [2]. Firstly, there is activation of extrinsic pathway secondary to release of tissue factor and cancer pro-coagulant from malignant cells. Secondly, there is increased annexin II receptor expression on the surface of the leukemic promyelocytes [3]. Annexin II receptor binds plasminogen and tissue plasminogen activator and increases plasmin formation by a factor of 60, thereby leading to increased

fibrinolysis. Thirdly, there is increased non-specific proteolysis leading to increased bleeding tendency [2]. Though bleeding tendencies are the more common presentation in APL, prothrombotic state is also seen in APL [4]. Paradoxically ATRA which induces complete remission in majority of cases and rapidly reverses coagulopathy has been implicated in prothrombotic state [5]. In two large scale studies incidence of thrombosis has varied from 4.5 to 5.6% [6, 7]. Table 1 summarizes clinical details of patients of APL presenting with thrombosis. Postulated mechanisms include release of cytokines subsequent to initiation of treatment [2] and rapid correction of fibrinolysis by ATRA inducing a prothrombotic state [6]. A high TLC, bcr3 (short) isoform of PML-RAR α transcripts, FLT3 ITD, expression of CD 2 and CD 15 on leukemic cells have been found to be associated with increased risk of thrombosis [7]. Our patient had presented with ischemic infarct before initiation of any treatment which makes it a rare presentation. Almost any organ can be affected with thrombosis. There are case reports of patients presenting with acute myocardial infarction and also ischemic stroke [7–9]. Rarely presentation may be with acute Budd-Chiari syndrome [10]. Presentation with thrombotic event portends a poor prognosis as was seen in our patient. Additional mechanisms predisposing to prothrombotic state besides ATRA need to be further elucidated in similar cases.

References

1. Warrell RP Jr, de The H, Wang ZY et al (1993) Acute promyelocytic leukemia. *N Engl J Med* 329:177–189
2. Barbui T, Finazzi G, Falanga A (1998) The impact of all-trans-retinoic acid on the coagulopathy of acute promyelocytic leukemia. *Blood* 91:3093–3102
3. Menell JS, Cesarman GM, Jacovina AT, McLaughlin MA, Lev EA, Hajjar KA (1999) Annexin II and bleeding in acute promyelocytic leukemia. *N Engl J Med* 340:994–1004
4. Falanga A, Barbui T (2001) Coagulopathy of acute promyelocytic leukemia. *Acta Haematol* 106:43–51
5. Runde V, Aul C, Heyll A et al (1992) All-trans-retinoic acid: not only a differentiating agent, but also an inducer of thromboembolic events in patients with M3 leukemia. *Blood* 79:534–535
6. Montesinos P, de la Serna J, Vellenga E et al. (2006) Incidence and risk factors for thrombosis in patients with acute promyelocytic leukemia. Experience of PETHEMA LPA 96 and LPA 99 protocols. *Blood (ASH annual meeting abstracts)* 108:1503
7. Breccia M, Avvisati G, Latagliati R et al (2007) Occurrence of thrombotic events in acute promyelocytic leukemia correlates with consistent immunophenotypic and molecular features. *Leukemia* 21:79–83
8. Lou YJ, Mai WY, Jin J (2006) Simultaneous presentation of acute myocardial infarction and acute promyelocytic leukemia. *Ann Hematol* 85:409–410
9. Quadir TA, Dhabhar BN, Dhar AK et al (1993) Acute promyelocytic leukemia with ischemic events. *J Assoc Physicians India* 41:300–302
10. Bandyopadhyay S, Bandyopadhyay D (2010) Acute Budd-Chiari syndrome as an initial presentation of acute promyelocytic leukemia. *J Cancer Res Ther* 6:567–569
11. Escudier SM, Kantarjian HM, Estey EH (1996) Thrombosis in patients with acute promyelocytic leukemia treated with and without all-trans-retinoic acid. *Leuk Lymphoma* 20:435–439
12. Pogliani EM, Rossini F, Casaroli, Maffe P, Corneo G (1997) Thrombotic complications in acute promyelocytic leukemia during all-trans-retinoic acid therapy. *Acta Haematol* 97:228–230
13. Hashimoto S, Koike T, Tatewaki W et al (1994) Fatal thromboembolism in acute promyelocytic leukemia during all-trans-retinoic acid therapy combined with antifibrinolytic therapy for prophylaxis of hemorrhage. *Leukemia* 8:1113–1115
14. Brown JE, Olujuhunbe A, Chang J et al (2000) All-trans-retinoic acid (ATRA) and tranexamic acid: a potentially fatal combination in acute promyelocytic leukemia. *Br J Haematol* 110:1010–1012
15. Colovic M, Miljic P, Colovic N et al (2001) Reversible portal vein thrombosis complicating induction therapy of acute promyelocytic leukemia. *Thromb Res* 101:101–103
16. Forjaz De Lacerda J, Alves Do Carmo J et al (1993) Multiple thrombosis in acute promyelocytic leukemia after tretinoin. *Lancet* 342:114–115
17. Assouline D, Negrier C, Coquard I et al (1995) Successful systemic thrombolysis of hepatic vein thrombosis in a patient with promyelocytic leukemia treated with all-trans-retinoic acid. *Am J Haematol* 48:291–292
18. Torromeo C, Latagliata R, Avvisati GF (1999) Coronaric thrombotic events in acute promyelocytic leukemia during all-trans-retinoic acid treatment: a role for adhesion molecules overexpression? *Leukemia* 13:312–313
19. Torromeo C, Latagliata R, Avvisati G et al (2001) Intraventricular thrombosis during all-trans-retinoic acid treatment in acute promyelocytic leukemia. *Leukemia* 15:1311–1313
20. Goldschmidt N, Gural A, Yehuda DB (2003) Extensive splenic infarction, deep vein thrombosis and pulmonary emboli complicating induction therapy with all-trans-retinoic acid (ATRA) for acute promyelocytic leukemia. *Leuk Lymphoma* 44:1433–1437