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Acute renal cortex necrosis caused by arterial thrombosis during treatment for acute promyelocytic leukemia

A 24-year old woman with a severe hemorrhagic diathesis was diagnosed with acute promyelocytic leukemia (APL). Treatment with all-trans retinoic acid (ATRA) and tranexaminic acid was started followed by idarubicin. The next day renal impairement was noted finally resulting in anuria and severe azotemia. She also experienced diminished consiousness, hypoxia, pleural effusions, weight gain and peripheral edema. Because ATRA-syndrome was supected, ATRA was stopped and treatment with corticosteroids was initiated. Despite these measures renal failure persisted, for which hemodialysis was started. A renal biopsy, taken 5 weeks after start of the treatment, demonstrated renal artery thrombosis and cortex necrosis probably due to tranexaminic acid therapy in combination with ATRA. This was confirmed by cortical atrophy and wedge-shaped cortical perfusion deficits demonstrated by CT-angiography. In patients with APL, receiving ATRA in combination with anti-fibrinolytic therapy, one should be aware of rare but life-threatening thrombotic complications. In case of rapidly progressive renal failure acute renal cortex necrosis should be considered

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Introduction. Bleeding complications are well known causes of morbidity and mortality in patients with acute promyelocytic leukemia (APL). For this reason patients are often treated with anti-fibrinolytic drugs, besides the anti-leukemic treatment with all-trans retinoic acid (ATRA) and anthracyclin-based chemotherapy. The combination of antifibrinolytics and ATRA however, can sometimes lead to thrombotic complications. We describe a unique patient with acute renal failure, commencing immediately after start of treatment, caused by cortex necrosis due arterial thrombosis.

Case report. A 24-year old woman was referred to our hospital because of hemorrhagic diathesis, i.e. spontaneous hematomas with diameter of more than 20 cm and epistaxis. Laboratory examination revealed mild anemia (hemoglobin 6.3 mmol/l) and leukopenia (leukocytes 3,1x10^9/L) and severe thrombocytopenia (platelets 7x10^9/L) (Tabel 1.). Coagulation studies showed a markedly decreased fibrinogen level, high D-dimer levels and reduced ±2-antiplasmin levels indicating hyperfibrinolysis. Other coagulation tests (APTT, PT and antithrombin) were normal. Bone marrow examination, which was complicated by severe blood loss (2 mmol/L hemoglobin level decrease), revealed an acute promyelocytic leukemia (APL) based on the abundant presence of typical promyelocytes (80%) with Auer rods. Cytogenetic and molecular diagnostic examination showed t(15;17) and PML-RAR fusion protein. Treatment with all-trans retinoic acid (ATRA) in combination with tranexaminic acid and corticosteroids was started immediately, followed by Idarubicin 12 mg/m^2 the next day according to the PETHEMA LPA-99 protocol. During the second day mild azotemia was noted (creatinin 135 mcmol/L, urea 9.0 mmol/L) and urinary output was diminished to less than 1000 ml. Ultrasound examination of the kidneys showed no structural abnormalities and arterial and venous doppler signs were present. Because of the differential diagnosis of acute tumor lysis syndrome (rise in LDH and phosphate) Idarubicin was stopped, hydration was hightened and rasburicase (recombinant urate oxidase) was started. Despite these measures anuria developed and patient deteriorated. She experienced weight gain, hypoxia, pleural effusions, peripheral edema and diminished consiousness, which was compatible with the ATRA-syndrome. ATRA was stopped on day 3, tranexaminic acid was stopped, high dose dexamethason was started and patient was admitted to the ICU. Five days after the start of treatment for APL hemodialysis had to be started because of a 20 kilogram weight gain, hypertension and severe azotemia (creatinin 724 mcmol/L and urea 32.9 mmol/L). After stopping for 4 days the Idarubicin was given another 3 times to finish the first cycle of chemotherapy while patient underwent hemodialysis and ATRA was restarted after 2 weeks. After the first cycle of chemotherapy APL was in complete remission based on cytomorphologic criteria. Molecular diagnostics showed no PML-RAR fusion protein and the coagulation disorders were normalized (Tabel 1). Unfortunately the renal failure persisted, for which she is still receiving hemodialysis 3 times a week. After normalization of the coagulation disorders a needle biopsy from the kidney was performed 5 weeks after the start of chemotherapy. This biopsy revealed severe acute cortex necrosis with intact medullar tubuli and thrombosis in several middle sized arteries in the cortex (Figure 1A and 1B). A repeated ultrasound examination of the kidneys revealed no struc-

Table 1.

	Day 0	Day 2	Day 4	Day 30	*Normal*
Hemoglobin	6.3	4.5	5.3	6.0	*7.5-9.5 mmol/l*
Platelets	24	11	26	140	*150-370 x 10^9*
Leucocytes	3.1	6.1	5.5	2.0	*4.5-10.9 x 10^9*
Uric acid	-	0.40	<0.01	-	*0.15-0.45 mmol/l*
Phosphate	1.13	1.44	2.1	1.06	*0.6-1.2 mmol/l*
Creatinin	59	135	724	655	*55-90 mcmol/l*
LDH	398	1488	>121	758	*0-449 U/l*
PT	14.2	17.0	16.4	13.9	*10.9-13.3 sec.*
APTT	33	27	34	31	*26-39 sec*
Fibrinogen	1.1	0.5	2.2	2.8	*1.5-3.6 g/l*
D-dimer	8.2	11.6	2.6	1.1	*0.09-0.25 mg/l*
Antithrombin	1.18	1.03	0.90	1.06	*0.8-1.2 U/l*
Antiplasmin	0.60	0.42	0.52	1.15	*0.8-1.2 U/l*

tural abnormalities and still normal venous and arterial doppler signs were found. A CT-angiography of the kidneys, executed 2 months after start of the chemotherapy, demonstrated cortical atrophy and wedge-shaped cortical perfusion deficits, without any signs of occlusion from the large renal arteries (Figure 2).

Discussion. Primary or secondary (to disseminated intravascular coagulation) hyperfibrinolysis is frequently seen in patients with APL probably caused by the release of leukocyte proteases from the promyelocytes resulting in plasmin activation.[1;2] Another, more recently described, mechanism of increased production of plasmin is the high level of expression of annexin II on the surface of APL cells.[3] Annexin II is a cell-surface receptor for both plasminogen and tissue plasminogen activator (t-PA). Overexpression of annexin II may therefore contribute to activation of the fibrinolytic system in APL. Hyperfibrinolysis may result in life-threatening bleeding complications with mortality rates up to 30%.[4] Because of this life threatening situation ATRA and anthraclin based chemotherapy should be started immediately to which antifibrinolytic therapy may be added in case of hyperfibrinolysis, low platelet count (<50x10^9/L) and active bleeding. Despite DIC features in nearly all

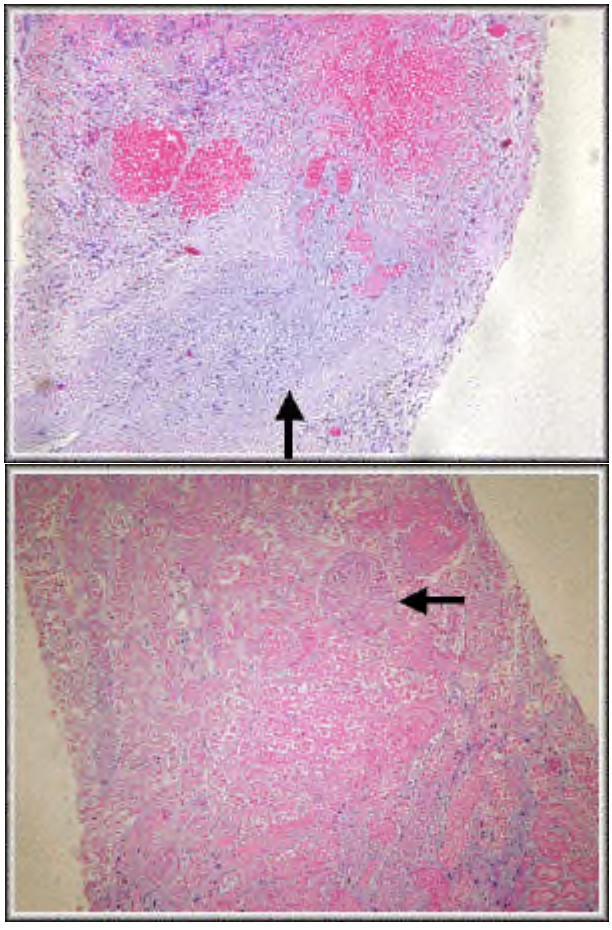

Figure 1a. and 1b.

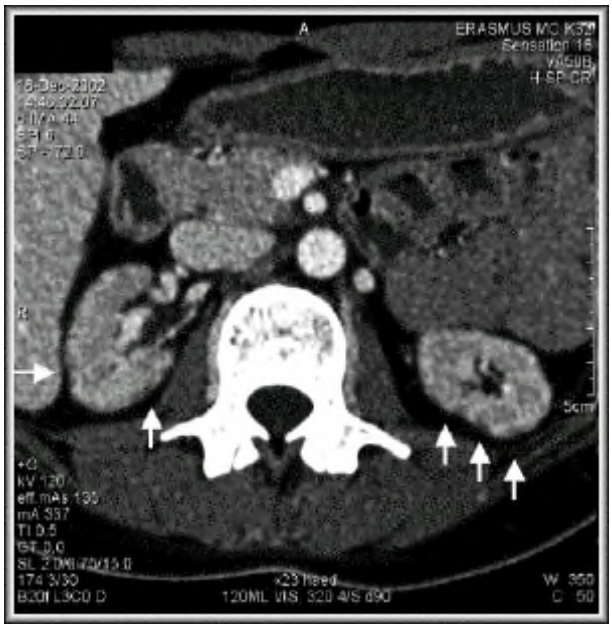

Figure 2.

patients with APL, caused by thrombin activating substances from leukemic cells, thrombotic complications are seen infrequently in patients treated with chemotherapy alone.[7] In patients treated with both ATRA and antifibrinolytc drugs bleeding complications are effectively diminished, however thrombosis may be seen more frequently.[4,7] Sometimes thrombosis can be in life threatening or even fatal. Several authors therefore recommend not to use this combination or only cautiously in patients with APL.[8,9] The paradox of bleeding and thrombosis may be explained by the disappearence of the hyperfibrinolysis after 4 to 7 days during treatment with ATRA resulting in a persistent procoagulant state.[6,10,11] This clinical observation is substantiated by studies of Mendell et al, who showed that after five days of ATRA treatment plasmin overexpression decreased to normal levels, which was preceded by normalized cellular expression of annexin II.[3] Therefore it is advised to discontinue antifibrinolytic treatment after 4 to 5 days. Some even suggest to administer heparin prophylactically after 5 days of treatment.[1,7] Renal failure in patients with APL is rarely encountered during treatment, but the causes can be diverse, including tumor lysis syndrome, ATRA-syndrome and sepsis. Several authors have described the increased risk of renal impairement with the application of ATRA,[7,12] mostly caused by the ATRA syndrome.[13] A rare cause of renal impairement during treatment with ATRA is thrombosis of renal vessels.[4,7] We have found two case reports of patients with APL who died during treatment with ATRA in combination with antifibrinolytic drugs. Post mortem examination revealed generalized microthrombi and occlusions of microcapillaries, including the kidneys. Acute cortex necrosis was well documented in our patient by histo-

logic examination of renal biopsy and visualized by CT-angiography. No reversibility of renal failure was observed during 4 months of follow-up resulting in prolonged hemodialysis three times a week. This case demonstrates that even in the presence of severe hyperfibrinolysis and active bleeding in a patient with APL one should be careful to administer antifibrinolytic drugs in combination with ATRA, because of the risk of severe thrombosis. In the case of rapidly progressive renal failure during treatment of patients with APL one should consider acute cortex necrosis and anti-fibrinolytic drugs should be discontinued immediately.

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References

1. Dombret H., Scrobohaci M.L., Daniel M.T., Miclea J.M., Castaigne S., Chomienne C., Fenaux P., Degos L. In vivo thrombin and plasmin activities in patients with acute promyelocytic leukemia (APL): effect of all-trans retinoic acid (ATRA) therapy. Leukemia 1995 1: 19-24
2. Kwaan H.C., Wang J., Boggio L.N. Abnormalities in hemostasis in acute promyelocytic leukemia. Hematol. Oncol. 2002 20: 33-41
3. Menell J.S., Cesarman G.M., Jacovina A.T., McLaughlin M.A., Lev E.A., Hajjar K.A. Annexin II and bleeding in acute promyelocytic leukemia. NEJM 1999 340: 994-1005
4. Escudier S.M., Kantarjian H.M., Estey E.H. Thrombosis in patients with acute promyelocytic leukemia treated with and without all-trans retinoic acid. Leuk. Lymphoma 1996 5: 435-9
5. Tallman MS, Andersen JW, Schiffer CA, Appelbaum FR, Feusner JH, Woods WG, Ogden A, Weinstein H, Shepherd L, Willman C, Bloomfield CD, Rowe JM, Wiernik PH. All-trans retinoic acid in acute promyelocytic leukemia: long-term outcome and prognostic factor analysis from the North American Intergroup protocol. Blood 2002;100;4298-302
6. Falanga A., Barbui T. Coagulopathy of Acute Promyelocytic Leukemia. Acta Hematologica 2001 106: 43-51
7. Pogliani E.m., Rossini F., Casaroli I., Maffe P., Corneo G. Thrombotic complications in acute promyelocytic leukemia during all-trans retinoic acid therapy. Acta Haematol 1997 4: 228-30
8. Hashimoto S., Koike T., Tatewaki W., Seki Y., Sato N., Azegami T., Tsukada N., Takahashi H., Kimura H., Ueno M., et al. Fatal thromboembolism in acute promyelocytic leukemia during all-trans retinoic acid therapy combined with antifibrinolytic therapy for prophylaxis of hemorrhage. Leukemia 1994 7: 1113-5
9. Mahendra P., Keeling D.M., Hood I.M., Baglin T.P. Marcus R.E. Fatal thromboembolism in acute promyelocytic leukemia treated with all-trans retinoic and aprotinin. Br. J. Haematol. 2000 110: 1010-12
10 Avvista G., Cate ten J.W., Sturk A., Lamping R., Petti M.G., Mandelli F. Acquired alpha-2-antiplasmin deficiency in acute promyelocytic leukemia. Br. J. Haematol. 1988 1: 43-8
11 Watanabe R., Murata M., Takayama N., Tokuhira M., Kizaki M., Okamoto S., Kawai Y., Watanabe K., Murakami H., Kikuchi M., Nakamura S., Ikeda Y. Long-term follow-up of hemostatic molecular markers during remission induction therapy with all-trans retinoic acid for acute promyelocytic leukemia. Keio Haematology-Oncology Cooperative Study Group (KHOCS). Thromb. Haemost. 1997 4: 641-5
12 Wang Z.Y., Chen Z., Huang W., Li X.S., Lu J.X., Huang L.A., Zhang F.Q., Gu L.J., Ouyang R.R., Chen S.J., et al. Probelms existing in differentiation therapy of acute promyelocytic leukemia (APL) with all-trans retinoic acid (ATRA). Blood cells 1993 3: 633-41
13 Flombaum C.D., Isaacs M., Reich L., Berman E., Warrell R.P. Acute renal failure associated with the retinoic acid syndrome in acute promyelocytic leukemia. Am. J. Kidney Dis. 1996 1: 134-7