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ПРИКАЗ БОЛЕСНИКА / CASE REPORT
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Acute Myocardial Infarction during Induction Chemotherapy for Acute *MLL t*(4;11) Leukemia with Lineage Switch and Extreme Leukocytosis

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SUMMARY

Introduction In patients with acute leukemias hemorrhage is the most frequent problem. Vein thrombotic events may appear rarely but arterial thromboses are exceptionally rare. We present a patient with acute leukemia and bilateral deep leg vein thrombosis who developed an acute myocardial infarction (AMI) during induction chemotherapy. The etiology and treatment of AMI in patients with acute leukemia, which is a rare occurrence, is discussed.

Case Outline In April of 2012 a 37-year-old male presented with bilateral deep leg vein thrombosis and malaise. Laboratory data were as follows: Hb 118 g/L, WBC 354×10^9/L (with 91% blasts in differential leukocyte count), platelets 60×10^9/L. Bone marrow aspirate and immunophenotype revealed the presence of acute lymphoblastic leukemia. Cytogenetic analysis was as follows: 46,XY,t(4;11)(q21:q23)[2]/62-82,XY,t(4;11)[18]. Molecular analysis showed *MLL-AF4* rearrangement. The patient was on low molecular weight heparin and combined chemotherapy according to protocol HyperCVAD. On day 10 after chemotherapy he got chest pain. Three days later AMI was diagnosed (creatine kinase 66 U/L, CK-MB 13U/L, troponin 1.19 μg/L). Electrocardiogram showed the ST elevation in leads D1, D2, aVL, V5 and V6 and "micro q" in D1. On echocardiography, hypokinesia of the left ventricle and ejection fraction of 39% was found. After recovering from AMI and restoring left ventricle ejection fraction to 59%, second course of HyperCVAD was given. The control bone marrow aspirate showed 88% of blasts but with monoblastic appearance. Flow cytometry confirmed a lineage switch from lymphoblasts to monoblasts. In further course of the disease he was treated with a variety of chemotherapeutic combinations without achieving remission. Eventually, palliative chemotherapy was administered to reduce the bulk of blasts. He died five months after the initial diagnosis.

Conclusion AMI in young adults with acute leukemia is a very rare complication which may occur in patients with very high white blood cell count in addition with presence of a CD56 adhesion molecule and other concomitant thrombophilic factors. The treatment of AMI in patients with acute leukemias should include antiplatelet and anticoagulant therapy, even with more aggressive methods depending on patient's age and clinical risk assessment.

Keywords: acute myeloid leukemia; chest pain; myocardial infarction; chemotherapy; leukocytosis

INTRODUCTION

Although hemorrhagic diathesis usually accompany acute leukemias, thrombotic events may occur at diagnosis, or later during the course of the disease. Thromboses are described most frequently in connection with acute promyelocytic and acute lymphoblastic leukemia, in which treatment with all-trans-retinoic acid or L-asparaginase causes impairment of anticoagulant mechanisms producing prothrombotic state [1, 2]. But in other types of acute myeloid leukemias (AML) the thrombosis is not negligible, as it was found in 3.2% of patients at presentation [2].

Multiple prothrombotic factors have been identified including effects of antileukemic therapy [3], hyperleukocytosis [3, 4, 5], heritable thrombophilias [6], indwelling central vein catheters and an acquired hypercoagulable state as antiphospholipid syndrome, heparin-induced thrombocytopenia and disseminated intravascular coagulation (DIC) [7].

Arterial thromboses are extremely rare as most thrombotic events occur in veins. Acute myocardial infarctions (AMI) in younger patients with AML were rarely reported [3-7]. We present a patient with a rare acute leukemia associated with t(4;11)(q21:q23), switched immunophenotype from acute lymphoblastic to acute monoblastic lineage, in whom AMI developed during the course of induction chemotherapy. According to PubMed survey of the world literature, there are 11 reported cases, but, to the best of our knowledge, this is the first case of AMI associated with a lineage switch acute leukemia.

CASE REPORT

A 37-year-old male presented in April of 2012 with a history of four-week bilateral thrombosis of deep leg veins. He was put on low molecular weight heparin (LMWH) and cardiopirin. During regular checkups, leukocytosis was noticed

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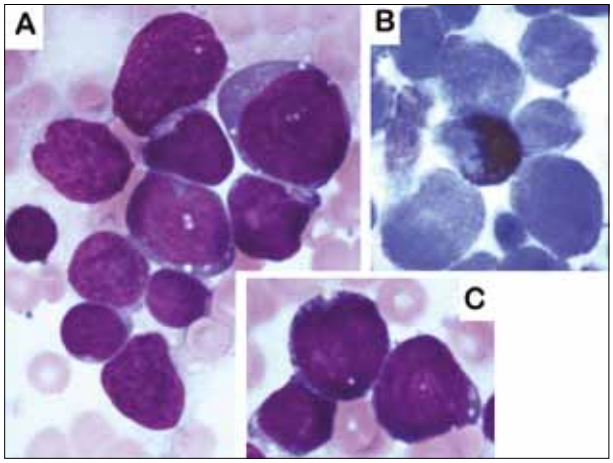

Figure 1. Bone marrow cytology at diagnosis. Leukemic cells are polymorphous, with scarcely basophilic cytoplasm, without azurophilic granules. (A and C, MGG, 1000×). Myeloperoxidase staining is negative (B, POX, and 1000×).

and hospitalization was advised to him. His past medical history was unremarkable, without any cardiologic past history. He had smoked 20 cigarettes a day for eight years. On the day of admission, on April 30, 2012, physical examination revealed normal vital signs and petechiae. The liver and spleen were palpable at the costal ribs. Initial laboratory work-up was significant for a low platelet count of 60×10^9/L, hemoglobin 118 g/L, and white blood cell (WBC) count of 354×10^9/L with blasts 94%. Blood biochemistry was within normal limits except for a lactic dehydrogenase level of 22,642 U/L. Hemostatic tests were as follows: fibrinogen 2.16 g/L, prothrombin time 52%, activated partial thromboplastin time (aPTT) 24.4s, D-dimer 35.2 μg/L, the International Society of Thrombosis and Haemostasis score for DIC was 5. Abdominal ultrasonography revealed enlarged both the liver (168 mm) and the spleen (138 mm). Conventional cytogenetic analysis showed 46,XY, t(4;11)(q21:q23)[2]/62-82,XY, t(4;11)[18]. A bone marrow aspirate was hypercellular with 91% of mononuclear blasts which were myeloperoxidase and periodic-acid-Schiff negative, consistent with acute lymphoblastic leukemia, L2 type according to the French–American–British classification (Figure 1) [8].

Immunophenotype of the mononuclear marrow cells disclosed a population of blasts HLA-DR, CD38, nTdT, CD19, CD22, cCD79a, cIgM, CD15+, which was in accordance with cytomorphologic type of leukemia. He was started with 6-mercaptopurine and prednisolone until the drop in WBCs to 60×10^9/L. On May 5, 2012, the protocol Hyper-CVAD (cyclophosphamide 600 mg in D1, D2 and D3, Dexasone 40 mg in D1–D14, Daunoblastin 40 mg in D4, Vcr 2 mg in D4 and D11, with G-CSF in D3–D21) was administered, with intrathecal prophylaxis. On the seventh day of the protocol WBCs dropped to 0.6×10^9/L and the patient developed fever. Broad spectrum antibiotics (meronem, vancomycin, Diflucan, and G-CSF) were introduced. Ten days after the beginning of chemotherapy (May 15, 2012) the patient developed chest pain, became hypotensive, with systolic blood pressure of 85 mmHg. The ECG at that time was normal. Myocardial enzymes were not elevated (CK 26 U/L, CK-MB12 U/L, troponin 0.190 μg/L). Dopamine infusions and nitroglycerin tablets were administered. The next day the chest pain persisted, but during that day the enzymes and ECG, that were monitored, didn't show evolution to myocardial infarction. On the third day the patient was transferred to Emergency Unit as the chest pain did not stop. The ECG showed ST-elevation myocardial infarction in leads D1, D2, aVL, V5 and V6 with micro q in D1. At the same time cardiac biomarkers were tested and the results showed elevation (CK 66 U/L, CK-MB 13 U/L, troponin 1.19 μg/L). These findings corresponded to an anterolateral AMI (Figure 2) with a second-degree AV block. Echocardiography showed hypokinesia of the left ventricle, with the ejection fraction of 39%. In the cavity of the left ventricle there was an echo contrast showing presence of prethrombotic mass without clear signs of thrombus formation. The patient was treated with infusions of dopamine, oxygen, LMWH, carvedilol 12.5 mg (2 × ¼ tab.), diuretics, G-CSF, antibiotics (vancomycin, tienam, acyclovir, ciprocinal). Cardiac catheterization and percutaneous coronary intervention was offered to the patient, however he refused, preferring conservative medical treatment as he knew the main diagnosis of acute leukemia. Antiplatelet therapy was contraindicated because of the increased risk of bleeding due to thrombocytopenia. Also ACE-inhibitors were not given as the patient was hypotensive because of weakened left ventricular ejection fraction. During the next ten days WBC count increased from 0.7×10^9/L to 3.4×10^9/L, platelets increased from 19×10^9/L to 78×10^9/L. The patient recovered after ten days, chest

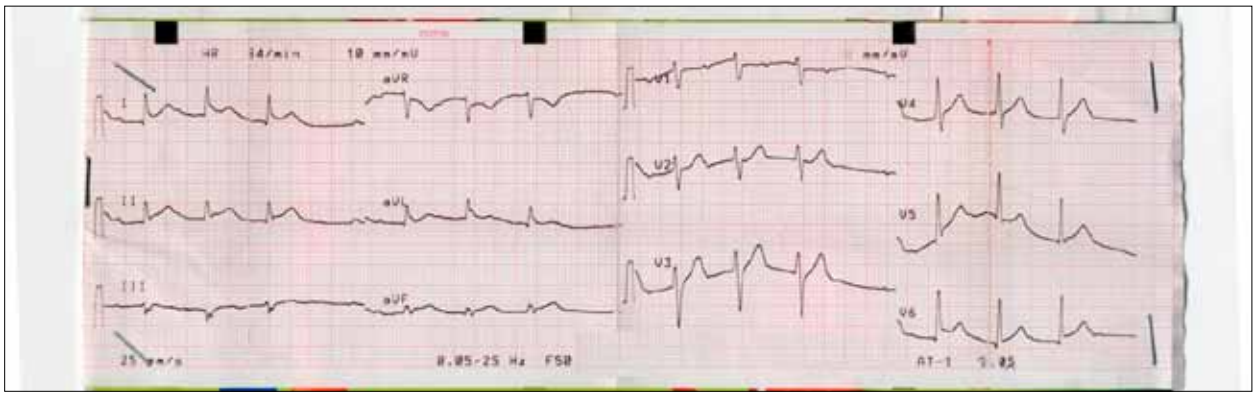

Figure 2. Electrocardiogram showing ST segment elevation in leads D1, D2, aVL, V5 and V6 with micro q in D1

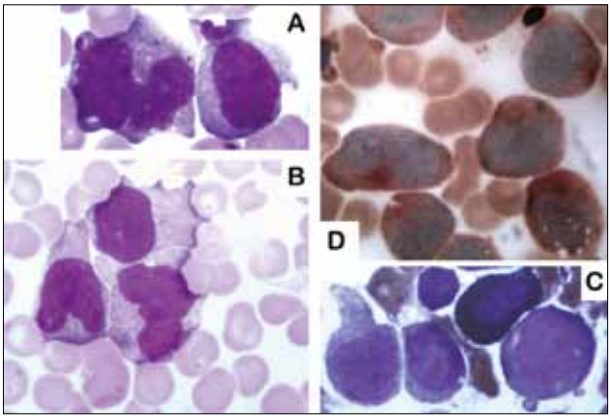

Figure 3. Bone marrow cytology at the time of immunophenotype switch. Leukemic cells are polymorphous, occasionally with lobulated or reniform nucleus, moderate to abundant cytoplasm, rare vacuoles and azurophilic granules (A and B, MGG, 1000×). Myeloperoxidase staining negative (C, POX, 1000×). ANAE staining positive in cytoplasm and Golgi region in blast and monocytoid cells (D, ANAE, and 1000×)

pain disappeared, dopamine infusions were discontinued, and ECG changes resolved to normal. After a complete cardiologic recovery (including echocardiography ejection fraction improvement to 59%), he was transferred again to Clinic of Hematology, where the bone marrow aspirate examination showed 60% of blasts. He received a second cycle of the same protocol Hyper-CVAD (methotrexate 2,000 mg on D1, Cytosar 2 × 6 g on D2 and D3). After the recovery, the bone marrow contained 88% of blasts with monoblastic morphology, myeloperoxidase and PAS negative (Figure 3). There was a switch in the immunophenotype pattern from lymphoblasts to monoblasts (HLA-DR, CD38, CD33, CD15, cCD68, cLysozyme^{high}, CD11b, CD11c, CD64, CD36, CD24, CD56)$^{+}$. A minor population (0.1%) of (CD19+, CD79a+) cells were also found corresponding to leukemic B-cells, which predominated at the time of diagnosis. This evidence suggested the diagnosis of CD56+/ AML with monocytoid differentiation. Cytogenetic analysis showed also the evolution of karyotype (46,XY,t(4;11)(q21;q23))[19]/47,XY,t(4;11)(q21;q23),+C[1]. The patient was treated with HiDAC+DA (ara-C 2× 6 g in D1, D2 and D3 and Daunoblastin in D2, D4 and D6).

After this therapy his condition was complicated with severe aplasia and secondary bronchopneumonia, abscess of the spleen, pulmonary aspergillosis, but without any sign of cardiac dysfunction. The patient finally recovered and became afebrile, but with 17% residual blasts in the bone marrow. He was treated additionally with mitoxantrone and vepeside without achieving complete remission. Further on during its course, the disease was treated as a resistant one, with palliative chemotherapy (6-mercaptopurine) just to reduce the WBC count. He died five months after initial diagnosis without a recurrence of the cardiac disease.

DISCUSSION

AML is a hematopoietic stem cell disorder characterized by somatically acquired genetic changes in progenitor cells which alter the normal mechanism of proliferation and differentiation [9]. AML is classified according to WHO classification into several distinct entities depending on morphologic and molecular-genetic characteristics [10]. Acute leukemia with t(9;11)(p22:q23) may be found in 2% of adult patient population. These patients may present with DIC and extramedullary myeloid sarcomas within different tissues. A "lineage switch" phenomenon is occasionally observed within this high-risk group of patients when at the time of the initial diagnosis the disease meets the criteria for a lymphoid or myeloid leukemia with an opposite lineage at relapse [9, 11, 12]. When lineage switch is diagnosed, it may represent either the emergence of an independent ancestral leukemic clone or a relapse of the original clone with heterogeneity at the morphological level but usually more resistant to chemotherapy [9].

It is also well known that expression of CD56 molecules, which we observed in our patient's leukemic cell membrane, is an adverse prognostic factor with capability to adhere to cells in different tissues and as such might contribute to a local myeloid sarcomas' formation [13].

Our patient, without previous history of coronary disease, presented with extremely high WBC count and within 10 days of induction chemotherapy experienced an acute coronary STEMI event (ST segment elevation myocardial infarction), most probably caused by bulky tumor mass. We were not able to perform coronary angiography and find out the real cause of coronary artery occlusion, but our suspicion was a formation of leukemic thrombi as it is well-known that they represent a complication in patients with acute and chronic leukemias and high WBC count. Additional contributing thrombogenic factor was DIC and infection, and finally expression of adhesion CD56 molecules on leukemic cells, which modulates adhesion between leukemic cells and endothelium.

Reviewing the literature we found 11 relevant cases of AMI in patients with acute leukemias but with different etiopathogenetic mechanisms leading to coronary arterial occlusion [3-7, 14-19], including leukostasis syndrome, leukemic thrombus formation [3, 4, 5], less deformable blast cells contributing to atherothrombosis [14, 16], effects of antileukemic chemotherapy, DIC [4, 6, 7, 18], leukemic myocardial infiltration, preponderance of leukemic cells to adherence due to having CD56 molecule on cell surface, thrombocytopenia, and a possible hemorrhage into the myocardial wall or intimae of coronary arteries [7, 13] and deficiency of some coagulation and antithrombotic factors [6, 7]. Even in AML with normal WBC count STEMI may occur, but mechanisms of thrombotic vascular occlusion in such patients include alterations in microcirculatory rheology, increased adhesiveness of leukemic cells which are less deformable than corresponding mature cells, and increased procoagulant activity induced by cytokines [13].

It has also been found that coronary arteries vasospasms, which may be provoked by cytokines released from activated platelets, inflammatory cells or leukemic cells, play a significant role in occlusive coronary artery thrombosis [14]. Some chemotherapeutic agents have prothrombotic tendency such as L-asparaginase which induc-

es hypercoagulability and AMI which has been reported in patient with acute lymphoblastic leukemia, although in this report the authors suspect that contributing factor was administration of prednisone, vincristine and anthracyclines, which caused activation of coagulation and direct endothelial vascular damage [18]. Platelet-fibrin thrombus formation is possible in spite of thrombocytopenia [14, 18]. In circumstances of coronary arteries occlusion antithrombotic therapy should be carefully considered. Thrombolytic therapy was tried once, however the patient died due to fatal hemorrhage and such treatment is not recommended any more [17]. Usually dual antiplatelet therapy and anticoagulation should be administered as coronary arteries thrombi consist of platelets and fibrin. Administration of these drugs can prevent further clot progression [14]. However, concomitant AML and AMI are accompanied by thrombocytopenia and an increased risk of bleeding, so there is considerable danger of cardiac interventions, especially in circumstances of dual antiplatelet and anticoagulation therapy. This procedure could be recommended according to European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization only in patients in whom there is a chance of favorable outcome of antileukemic treatment and after rigorous preparations for the procedure [20]. The prognosis of AMI and AML is especially poor in the elderly, much more so than if either of the conditions appeared separately.

This report represents the first case of acute leukemia with hyperleukocytosis and the "lineage switch" phenomenon, from the acute lymphoblastic to acute monoblastic leukemia and STEMI. The case shows that a leukostatic coronary occlusion can occur in acute leukemia with extreme hyperleukocytosis, accompanied with DIC, infection, in association with the presence of adhesion molecules on leukemic cells in a relatively young patient without the preexisting coronary artery disease.

The study was approved by the Institutional Ethical Board.

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Акутни инфаркт миокарда током индукционог лечења *MLL t(4;11)* леукемије са линијском променом и екстремном леукоцитозом

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КРАТАК САДРЖАЈ

Увод Код болесника с акутним леукемијама најчешћи проблем су крварења. Врло ретко могу се јавити венске, а изузетно ретко артеријске тромбозе. Приказујемо болесника с акутном леукемијом и тромбозом дубоких вена на обе ноге код којег се током индукционе хемиотерапије развио акутни инфаркт миокарда (АИМ). У раду су разматрани етиологија и лечење АИМ код болесника с акутном леукемијом.

Приказ болесника Приказан је 37-годишњи болесник који се разболео априла 2012. године са дубоком венском тромбозом на обе ноге. Лабораторијске анализе су показале следеће: хемоглобин 118 *g/l*, леукоцити 354×10^9/*l* (са 91% бласта у диференцијалној леукоцитарној формули) и тромбоцити 60×10^9/*l*. Анализом ћелија аспирата костне сржи и проточном цитометријом постављена је дијагноза акутне лимфобластне леукемије. Цитогенетском анализом утврђен је кариотип *46,XY,t(4;11)(q21:q23)[2]/62-82,XY,t(4;11)[18]*, а молекуларна анализа је показала *MLL-AF4* реаранжман. Болесник је лечен нискомолекуларним хепарином и протоколом *HyperCVAD*. Десетог дана од почетка терапије јавио се бол у грудима, а трећег дана од појаве бола дијагностикован је АИМ с елевацијом *ST*-сегмента у одводима *D1*, *D2*, *aVL*, *V5* и *V6* и *micro q* у *D1*. На ехокардиографском налазу установљене су хипокинезија леве коморе и ејекциона фракција од 39%. Када се болесник потпуно опоравио, примењен је други циклус протокола *HyperCVAD*. Након аплазије костне сржи у контролном аспирату поново је нађено 88% бласта монобластног изгледа, што је потврђено и проточном цитометријом. Болесник је даље лечен разним комбинацијама хемотерапеутика којима се није могла постићи ремисија, те је на крају примењена палијативна терапија само ради смањења туморске масе. Пацијент је умро пет месеци након почетка болести.

Закључак АИМ код младих одраслих особа с акутном леукемијом је ретка компликација која се јавља код болесника с изразито високим бројем леукоцита уз присуство других тромбогених фактора, као што су експресија адхезионог молекула *CD56* на леукемијским ћелијама, дисеминована интраваскуларна коагулација, тромбоцитопенија и инфекција. Лечење АИМ се врши применом антитромбоцитне и антикоагулантне терапије, инвазивним процедурама уз одговарајућу припрему, и то уколико је реч о млађем болеснику, у зависности од процене исхода лечења акутне леукемије.

Кључне речи: акутна мијелоидна леукемија; бол у грудима; инфаркт миокарда; хемиотерапија; леукоцитоза

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