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CHRONIC MONOCYTIC LEUKOSIS WITH TRANSFORMATION INTO ACUTE MONOCYTIC LEUKEMIA

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Abstract. Chronic monocytic leukemia with transformation into acute monocytic leukemia. Shponka I.S., Pesotskaya L.A., Korolenko H.S., Hutnik I.O., Murashevych B.V., Nikonenko V.A. *Chronic myelomonocytic leukosis (CMML) is rarely diagnosed and amounts to 1 per 100 thousand of adults per year, more often in men over 60 years. The clinical case of the rare, prolonged course of myelodysplastic chronic myelomonocytic leukosis (MD-CMML) in a middle-aged woman with rapid transformation into acute monocytic leukemia (AMoL-M5в) with the atypical fulminant course is presented. A retrospective analysis of the course of the disease drew attention to the severe vasculitis suffered by the patient 19 years ago, which could be regarded as the debut of CML in the presence of characteristic pathological changes in the hemogram. Non-pronounced clinical manifestations in the form of moderate cervical lymphadenopathy, skin lesions in the form of transient erythema, spotty eruptions over the next 10 years, fit into the clinical picture of MD-CMML. A detailed picture of the disease was observed after viral infection, bronchitis, antibiotic therapy. Absence of significant blastemia and severe inhibition of normal hematopoiesis with expressed extramedular manifestations of the disease in the patient were not typical for the course of AMoL-M5b in this case. The progression of skin lesions was noteworthy, which gave reason for unfavorable prognosis. For several weeks, the spread of erythematous elements was observed throughout the body with itching, not controlled by antihistamines and corticosteroid drugs; the appearance of maculopapular rashes, merging in places; small-point hemorrhages like vasculitis over the entire surface of the skin. Notable was the development of severe hemorrhagic syndrome without severe thrombocytopenia, significant changes in the coagulogram, as a manifestation of early severe coagulopathy.*

Реферат. Хронічний моноцитарний лейкоз з трансформацією в гострий моноцитарний лейкоз. Шпонька І.С., Пісоцька Л.А., Короленко Г.С., Гутнік І.О., Мурашевич Б.В., Ніконенко В.А. *Хронічний мієломоноцитарний лейкоз (ХММЛ) діагностується рідко і складає щорічно 1 на 100 тис. дорослих, частіше в чоловіків старше 60 років. Представлений клінічний випадок складний для діагностики та лікування рідкісного, з тривалим перебігом мієлодиспластичного хронічного мієломоноцитарного лейкозу (МД-ХММЛ) у жінки середнього віку зі швидкою трансформацію в гостру моноцитарну лейкемію (ГМоЛ-М5в) з атиповим блискавичним перебігом. При ретроспективному аналізі перебігу захворювання звернено увагу на перенесений*

пацієнткою 19 років тому васкуліт з тяжким перебігом, що можна було розцінити як дебют ХММЛ, при наявності характерних патологічних змін у гемограмі. Невиражені клінічні прояви у вигляді помірної шийної лімфоаденопатії, ураження шкіри у вигляді минущих еритем, плямистих висипань протягом наступних 10 років укладалися в клінічну картину МД-ХММЛ. Розгорнута картина захворювання спостерігалася після вірусної інфекції, бронхіту. Не типовими для перебігу ГМоЛ-М5в були: відсутність значних бластемії і пригнічення нормального кровотворення при виражених екстрамедулярних проявах захворювання. Протягом декількох тижнів спостерігали поширення еритематозних елементів на всьому тулубі зі сверблячкою, що не зменшувалося за допомогою прийому антигістамінних і кортикостероїдних препаратів; поява плямисто-папульозних висипань, місцями зливних; дрібних крововиливів по типу васкуліту по всій поверхні шкіри. Примітним був розвиток вираженого геморагічного синдрому без значної тромбоцитопенії, істотних змін у коагулограмі, як прояв тяжкої коагулопатії.

Chronic myelomonocytic leukosis (CMML) is rarely diagnosed and amounts to 1 per 100 thousand adults annually. This disease occurs more often in men over 60 years, with a slowly progressing course [6, 11]. The etiology is multifactorial. The influence of external environmental factors is not excluded, in particular, radiation [9]. The main role is played by the genetic background, but no specific mutations have been found [2].

The morphological criteria of World Health Organization (2016, 2018) for CMML are: persistent peripheral blood (PB) monocytosis, >1000/μl with a percentage of monocytes ≥10% of leukocytes; blastosis in peripheral blood and bone marrow (BM) <20% (myeloblasts, monoblasts, promonocytes); dysplasia of ≥1 hematopoietic lineages with minimal dysplasia or its absence. Additional criteria: the presence of monocytosis from lasting ≥3 months with the exclusion of other causes of monocytosis. Subtypes of CML: 1 – myelodysplastic (MD-CMML) – leukocytosis ≤13000/μl; 2 – myeloproliferative (MP-CMML) – leukocytosis >13000/μl [1, 4, 6]. The most rare form is MD-CMML with monocytosis from mature cells in the PB and BM without inhibition of other hematopoietic lineages for a long period of time [6]. Clinical signs of the disease begin only after a few months, or even years. In the subsequent stages of the disease, an increase in the spleen and liver is observed. Lymph nodes are usually mildly enlarged with this pathology [6], the loss of appetite and body weight, low-grade fever or fever with night sweats, ossalgia, skin changes are observed in patient [9, 10, 12]. The skin reaction is usually a harbinger of disease progression and of the increase in the frequency of the transformation of the chronic process into acute myeloid leukosis (AML) [1, 3]. The morphological features of pathological cell forms in CMML when staining smears according to Romanovsky are “rugged” contours of monocytes and dysplasia of neutrophils [3, 6, 10, 11]. Also monocytes have a bizarre, bean-shaped nucleus and azurophilic granularity in the cytoplasm. A detailed picture of acute monocytic leukemia is accompanied by the appearance of monoblasts and promonocytes in the blood [1, 2]. Monoblasts are distinguished by the presence of a rounded nucleus with a thin lace chromatin, with a folding or lobed form, abundant or moderately developed, often basophilic cytoplasm. Promonocytes have a more sinuous outline of the nucleus, less basophilic cytoplasm and a large number of azurophilic granules. In a cytochemical study, monoblasts are myeloperoxidase (MPO) – negative [8, 11]. An oligomonocytic CMML representing a form of the disease of the early phase of the "dysplastic type" has been described by a number of authors. It is characterized by the younger age, the low number of leukocytes and the absolute number of neutrophils [12].

The treatment of patients with CML has certain difficulties, because some of them have a relatively indolent course of the disease with a median survival of more than 10 years, while in other cases the rapid progression of the disease is observed with the development of secondary AML resistant to the therapy. The median survival time of patients with MD-CMML is longer [3, 6]. Acute leukosis of monocytic origin (AML-M5), in which there is a high risk of CMML transformation, are rare (make up 3-6% of all AML) and difficult to diagnose due to the features of the clinical course. They differ for some time in an unexpressed clinical picture and insignificant morphological changes in the PB [7, 9]. According to the literature, prognostically unfavorable for the course of AML are the presence of preliminary MDS [8], specific skin lesions [5].

The aim of this work was to demonstrate the difficulties of diagnosing and treating chronic myelomonocytic leukemia, with an atypical long-term course, but rapid transformation into acute monocytic leukemia (AMoL-M5b) with an atypical fulminant course.

Woman T., 42 y.o., was staying in the hospital (hematology department) from 11/21/18 to 12/12/18 and from 12/15/18 to 12/31/18. Changes in the blood test were detected in the clinic during a routine examination in the absence of patient complaints. Outpatient for more than 10 years in the PB moderate leukocytosis (10-12 g/l) was observed with

monocytosis up to 12% without clinical manifestations. Therapy and consultation with a hematologist was not required. The patient underwent acute respiratory viral infections with acute bronchitis 2 weeks before admission to the hospital, for which she received antibacterial therapy. She was examined by an ENT doctor, rhinosinusitis was diagnosed. In connection with complaints of discomfort in the epigastric region, FGDS was performed – cicatricial deformity of the pyloric department, chronic active catarrhal gastroduodenitis; US examination of abdominal organs was performed – diffuse changes in the liver and pancreas. In a blood test in dynamics, increasing leukocytosis and monocytosis was found, in connection with which the woman was sent to a hospital for examination.

Oncological anamnesis is burdened. Father died of leukosis. The patient suffered a severe hemorrhagic vasculitis 19 years ago. In subsequent years, changes in the skin of the lower extremities have been periodically observed in the form of the increase in the vasculature, single small-spotted or spotted rashes from red to cyanotic or brown.

On the objective examination upon admission to the hospital, the patient's condition was regarded as moderate, taking into account changes in the blood. Physique and body weight are normal. Skin and mucous membranes of normal color. Cervical lymph nodes less than 1 cm were palpated, symmetrical, soft, not soldered to tissues, painless. The patient told that they appeared a long time ago and never bothered. Lungs and heart without features. Hepatomegaly (up to 6 cm below the edge of the costal arch) of moderate density, painless, had draw new attention, although according to the results of the ultrasound diagnostic, the size of the liver was normal. The spleen had not been palpable. A swelling on the legs were not observed. Bladder and bowel habits were normal. During 1 week of detoxification therapy, the patient's condition remained well, the size of the liver was reduced on 3 cm. However, erythema with mild itching appeared on the front surface of the chest, refractory to antihistamine and short-term corticosteroid therapy. According to the results of PB analyzes (Table), the progression of leukocytosis and monocytosis had been observed with a satisfactory clinical condition of the patient, and a slight degree of anemia had remained.

Peripheral blood indicators in dynamics

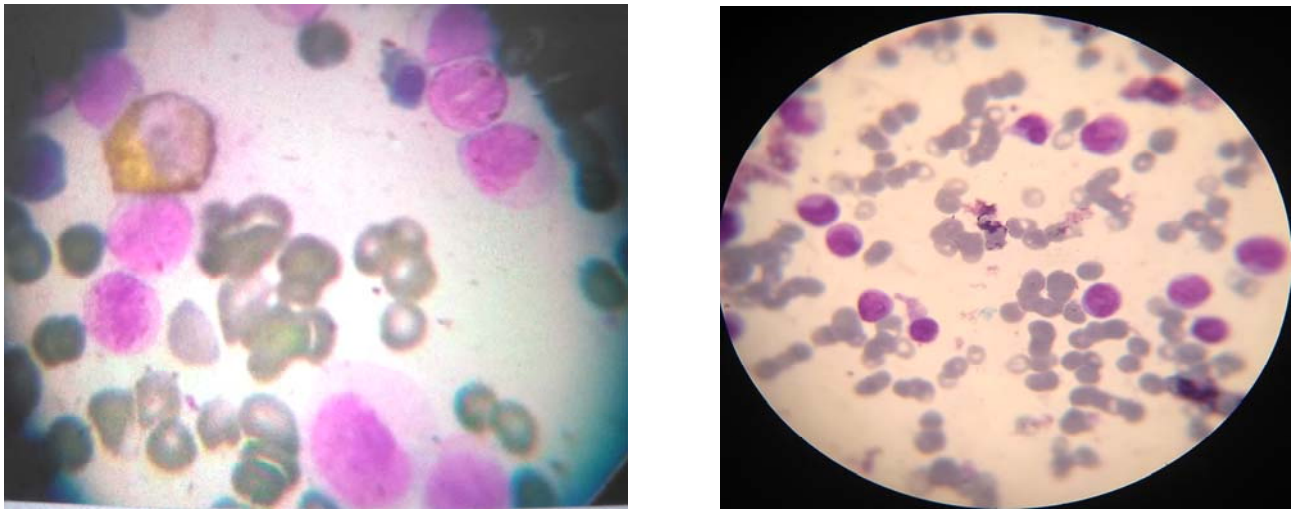
Indicators	22/11/18	26/11/18	30/11/18	7/12/18	16/12/18	20/12/18
RBC, 1012/l	3.5	3.5	3.5	3.6	3.4	2.9
Hemoglobin, g/l	107	108	107	109	102	92
Color indicator	0.97	0.92	0.92	0.92	0.9	0.89
WBC, 109/l	20.4	45.0	43.0	16.9	68.0	101.0
Eosinophiles, %	1	0	0	0	0	0
Basophiles, %	0	0	0	0	0	0
Blastes, %	0	0	0	1	2	9
N. myelocytes, %	1	1	4	5	6	6
N. metamyelocytes,%	1	1	3	2	3	2
N. bandes, %	3	4	2	2	1	1
N. matures, %	25	24	16	11	4	1
Lymphocytes, %	39	18	19	20	11	5
Promonocytes, %	0	0	0	0	20	30
Monocytes, %	30	52	56	59	53	51
Reticulocytes %	0,5	-	0,7	-	1,0	-
Plateletes, 109/l	227	-	231	-	120	100
ESR mm/hour	35	30	32	50	47	27

Note. N – neutrophils

To exclude acute leukosis, sternal puncture had been done. Myelogram counting results: blasts 4.0%, n. myelocytes 3.8%, n. metamyelocytes 4.6%, n. bandes 4.0%, n. mature 6.2%, eosinophiles 0.8%, lymphocytes 5.8%, monocytes 59.6%, plasmocytes 0.6%, proerythroblastes 0.2%, pronormoblastes 0.4%, basophillic normoblastes (nmb) 0.6%, polychromatic nmb 3.0%, orthochromatic nmb 6.4%. Megakaryocytes 2/100 cells, L/Er 8.4:1, n. maturation index 0.82, erythroblast maturation index 0.89, signs of dysplasia of cellular elements. Intense very small azurophilic granularity of the cytoplasma and atypia of monocytes had been noted, bizarre-shaped cells had been found. In some cells, the nuclei overlapped each other, as in blasts. But they had no characteristic signs of monoblasts: there were no nucleols, there was the more mature structure of the nucleus. The cytoplasm in some cells had a more basophilic color. Its edges were outlined, imitating mononuclear cells of monocytic type. The described cells could be classified as promonocytes.

According to the presented morphological data, there were no signs of acute leukemia, the dysplasia of the monocytic germ of the leukocyte series took place. The response to MPO was taken into account in monocytoid cells BM, because blast metaplasia was absent. In one-third of them, the reaction was weakly positive, which made it possible to establish the monocytoid rather than myeloid nature of the cells (Fig.).

A number of studies have been performed to rule out reactive monocytosis, which can occur in diseases of an infectious nature [2]. Upon admission, the reaction of microprecipitation of the blood is negative, biochemical parameters of glucose, renal and hepatic complexes are within normal limits, a general urine test without pathological changes. Blood test for the presence of the Epstein-Barr virus: immunoglobulin G more than 8 AE (more than 1.1 – positive); toxoplasma – antibodies G more than 650 IU/ml (more than 30 – positive), immunoglobulin M – negative. Markers of hepatitis B, C are negative; blood test for HIV – negative. Alpha phytoprotein, level of cancer embryonic antigen was normal. Multispiral computed tomography of abdominal organs, retroperitoneal space, chest and mediastinum with contrast: no signs of volumetric and inflammatory process had been detected. Signs of lymphoproliferative disease had not been detected. Hepatosplenomegaly, solitary simple cysts of the spleen and left kidney. The results of microbiological analysis of the bacterial culture from the nose and throat: nose – epidermal staphylococcus 10^6 had been detected, pharynx – no bacteria had been found, yeast-like fungi had been detected. Electrocardiography: sinus rhythm, heart rate 95, tachycardia, diffuse changes in the myocardium.



а **в**

А – the reaction of granules to peroxidase in individual bone marrow cells of the patient is weakly positive, в – monocytoid cells in a blood product

The patient had been examined by specialists: a gynecologist, surgeon, neurologist, rheumatologist, dermatologist, an infectious disease specialist (in dynamics). Data to confirm an infectious or primary somatic disease with reactive monocytosis have not been obtained.

After 10 days in the hospital, the patient's condition deteriorated sharply. A spotted vascular

pattern appeared with a small-pointed hemorrhagic rash (in some places – like hives) on the skin of the limbs, progressive sore throat, gums with swelling, which obstruct eating. Pain in the spine and lower extremities, febrile fever up to 39°C had been observed. The leukocytosis and monocytosis without cell rejuvenation persisted in the PB, but with signs of atypia, the number of granulocytes decreased; mild anemia persisted, too. A clinical diagnosis had been made: myelodysplastic syndrome with leukocytosis and significant monocytosis. Complications: intoxication, damage of gums, tonsils, liver, skin with hemorrhagic manifestations, with pain syndrome. Therapy had been started with small doses of Alexan, against the background of hemostatic, prophylactic antiulcer and antifungal infections, taking into account active gastritis according to the results of fibrogastroduodenoscopy and the detection of yeast during bacterial examination of the nose and throat.

The patient had been discharged from the hospital for outpatient treatment with slight clinical and laboratory improvement. There was no febrile fever, but subfebrile condition continued. Pain in the gums and throat, as well as the rash on the skin, decreased, the size of the liver decreased, and leukocytosis in the analysis decreased. However, high monocytosis without rejuvenation, but with signs of atypia, and anemia remained; neutropenia and ESR increased. It was recommended that the specific chemotherapy started should be continued outpatiently.

The patient had been hospitalized again 6 days after discharge from the hospital, but already in serious condition. Observations: fever to febrile marks; significant pain in throat and gums with their hyperplasia and ulcerative lesions of the oral mucosa, difficulty swallowing; pain in the whole body and spine. During the objective examination, a wide variety of papular and spotty rashes of different colors and sizes, sometimes of confluent character, had been discovered on the skin of the whole body. The cervical lymph nodes in the form of accumulations on both sides were significantly enlarged, slightly mobile, welded together, painless, 1.5-2 cm in diameter. The liver protruded from under the costal margin by 6 cm, moderately dense, painless. The spleen was palpated at the edge of the costal arch. There was no swelling on the legs, bladder and bowel habits were normal. Progressive leukocytosis and monocytosis had been observed in blood tests; blast cells, myelocytes, promonocytes had appeared. Red blood counts and platelets had decreased moderately (Table).

According to the WHO and Franco-American-British (FAB) classification of leukemia criteria and to the unified protocols of the Ministry of Health of Ukraine, acute monocytic leukosis M5b had been diagnosed [4]. The course of chemotherapy with cytarabin and doxirubicin had been performed. But, no positive effect had been obtained. The phenomena of intoxication, hemorrhagic, ulcerative-necrotic and proliferative syndromes, neuropathy from the spine and lower extremities with pain syndrome had been increasing. The severity of the condition had not allowed the continuation of the specific therapy. In the hemogram, leukocytosis, monocytosis, neutropenia had been progressing with a low percentage of blast elements. After 10 days, the patient died in the state of adynamia, the prevalence of sleep for several days. Postmortem autopsy had not been performed at the claim of relatives.

The peculiarity of our case was a rare, prolonged course of MD-CMML in a woman of middle age (according to the literature more typical for older men), with a transformation into a rare AMoL-M5b with an atypical fulminant course with lymphadenopathy and pronounced skin lesions.

A complex of corresponding examinations has been carried out to identify the primary diseases that cause leukemoid reactions (LR) of monocytic type. In our case, the progression of leukocytosis and monocytosis had been observed without a clinical picture of the acute process during 10 days. The assumption about LR had been excluded. According to morphological data of PB and BM, pursuant to WHO criteria, there had been the signs characteristic of 1-CMML: outpatient leukocytosis ≤13 g/L with monocytosis of more than 1000/μL in PB for a long time, the significant predominance of monocytic cells with signs of dysplasia in BM, in dynamics – monocytosis 6000/μl (30%) of the number of leukocytes (20 g/L) in PB, violation of the ratio between leukocyte and erythrocyte cells in BM with a decrease in the latter, a decrease in the absolute number of neutrophils in PB and BM. In this case, the course of the disease was not typical.

The retrospective analysis of the course of the disease drew attention to the severe vasculitis suffered by the patient 19 years ago, which could be regarded as the debut of CML in the presence of characteristic pathological changes in the PB. Moderate cervical lymphadenopathy, skin lesions in the form of transient erythema, spotty eruptions over the next 10 years, which fits into the clinical picture of MD-CMML. The pathological process progressed rapidly with transformation in AMoL after acute infection. The signs of neutrophil dysplasia, myeloid proliferation were not observed. Taking into account the literature data [9], all of the above admits the possibility of the presence of oligomonocytic CML

in the patient before the typical manifestation of MD-CML.

There were Auer rods in BM blasts is rare in CMML and is the unfavorable prognostic factor with rapid transformation into AML [11]. The absence of significant blastemia in PB and severe inhibition of normal hematopoiesis with pronounced extramedular manifestations of the disease and its rapid progression are not typical of primary AMoL, and were features of the pathological process in the described case, with previous CMML, monocytoid dysplasia, which occurs quite rare in AL [8]. Noteworthy is the change in the pathological elements of the skin during the progression of the disease.

The diagnostics had been complicated by the presence of a pronounced extramedullary lesion of the cervical lymph nodes with signs of lymphosarcomatous growth, in the absence of obvious morphological signs of blast metaplasia. There are few reports in the literature about patients with OMoL with extensive extramedullary leukemic tissue infiltration, as examples of true histiocytic "lymphomas" [11]. Due to the short duration of the course and the rapid progression of the disease, it had not been possible to carry out the necessary modern diagnostic immunophenotypic and immunohistochemical studies.

In the clinic of this case of secondary the progression of expressed hemorrhagic syndrome without severe thrombocytopenia, significant changes in the coagulogram, as the manifestation of the progression of severe coagulopathy was notable, which is associated with the FLT3 mutation [8]. Examination of the patient had revealed the increased level of IgG to toxoplasma, the immune response to which, at its time, apparently activated the macrophage system with possible somatic genetic mutations, against the background of the burdened hereditary genotype. The provoking factor for the clinical and laboratory manifestation of the new character of the disease, and possibly the mutagen, was the past ARVI of the respiratory tract. All prognostically unfavorable clinical signs described in the literature for the course of AMoL had been observed in our patient. However, the absence of initially high leukocytosis with a pronounced clinical picture and its fulminant course were atypical.

CONCLUSIONS.

1. The described clinical case of the rare MD-CMML with the transformation into the rare type of myeloid leukemia M5b of fulminant course, deserves the attention of clinicians in modern conditions of high mutagenic risk.
2. The presence of insignificant monocytosis in the peripheral blood, including asymptomatic character, requires careful dynamic observation of the patient by a general practitioner for timely referral to a consultation with a hematologist.

Conflict of interests. The authors declare no conflict of interest.

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