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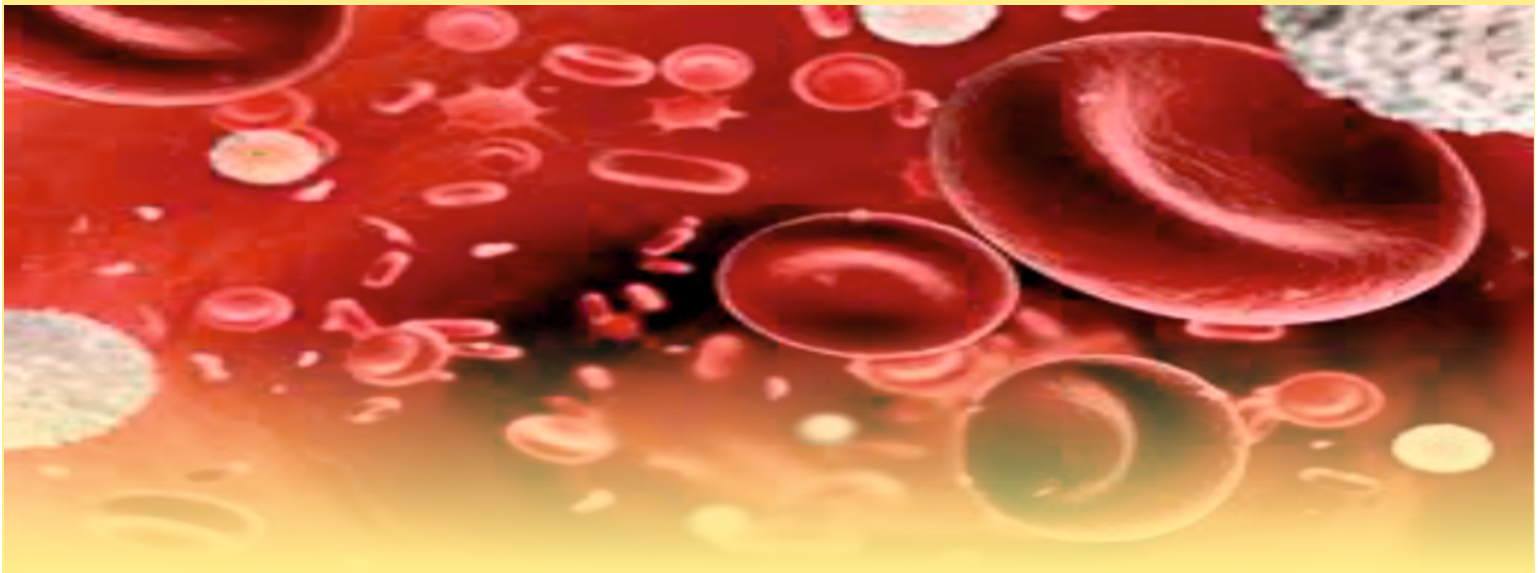
SOCIETATEA NAȚIONALĂ DE TRANSFUZIE SANGUINĂ DIN ROMÂNIA



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ROMANIAN SOCIETY OF HAEMATOLOGY

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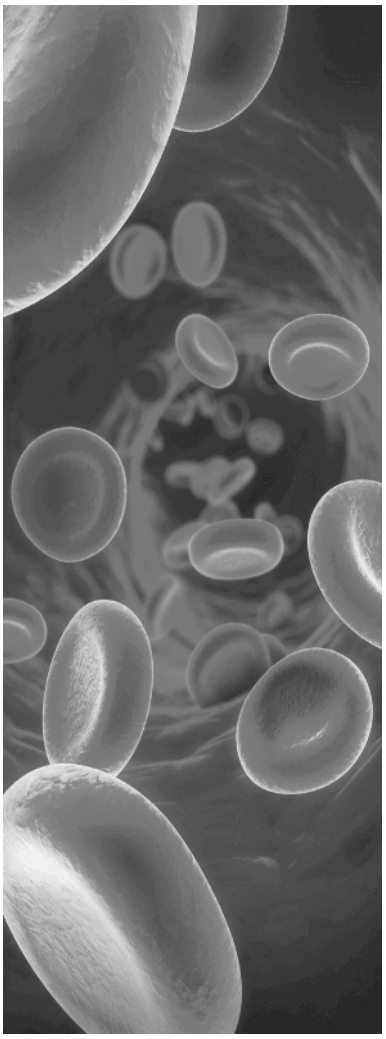

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Cytology of Central Nervous System relapse in Leukemias and Malignant Lymphomas

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1. Centre of Hematology and Bone Marrow Transplant, Fundeni Clinical Institute, Bucharest, Romania

Abstract:
The most commonly affected extra medullary site in acute leukemias and highly aggressive lymphomas types is the central nervous system (CNS). Cell counts and differentiation in cerebrospinal fluid is an important aspect in the process of finding the right diagnosis and with great impact over patient management.
Key words*: cerebrospinal fluid =CSF, relapse, central nervous system=CNS, cytology.*

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Cerebrospinal fluid it is a clear body fluid found in the brain and spinal cord, produced in the choroid plexuses of the ventricles of the brain. The CSF is derived from blood plasma and is largely similar to it, except that CSF is nearly protein-free compared with plasma and has some different electrolyte levels. CSF is normally free of red blood cells, and at most contains only a few white blood cells (0-5 leucocytes/ul: 40-80% lymphocytes, 15-45% monocytes and 0-6% neutrophils). Any white blood cell count higher than this constitutes pleocytosis.

Cell counts and differentiation in cerebrospinal fluid is an important aspect in the process of finding the right diagnosis and with great impact over patient management.

Pleocytosis can be caused by various infections, inflamations, chemical substances, neoplasia, vasculitis. In CSF one can also find neutrophils, eosinophils (in Hodgkin disease, parasitosis), lymphocytes, plasma cells, macrophages and tumor cells.

Cerebrospinal fluid analysis covers several analytical disciplines. This includes counting and differentiating cells and other particles. There are several advantages in automating these processes compared to manual methods using a traditional counting chamber. Because of the quick degradation of cells in body fluids, especially neutrophils, the sample must be analyzed as quickly as possible. A permissible time frame of 2 hours between the collection of the cerebrospinal fluid and the cell count is sometimes specified, but the cells (especially the neutrophil granulocytes) can already lyse within the first hour, which can decrease or falsify the value of the cell count. The shorter lifespan of the cells (especially granulocytes) in the cerebrospinal fluid, is attributable to the significantly lower protein content in the cerebrospinal fluid. Exposure to light or contact with oxygen can shorten the in vitro half life of granulocytes even more [1].

In our clinic CSF and other body fluids are processed with SYSMEX XN-2000 hematology analyzer. This new analyzer has a BF mode which measure body fluids. A white blood cell differential channel (WDF channel) can determine the white blood cell counts, differentiate their fraction, and detect abnormal cells through its optimized reagent reaction, signal processing, and analysis algorithms [1].

Cerebrospinal fluid can be collected in limited quantities. Usually laboratory diagnostics requires 5–10 mL, in which roughly 4–5 mL should be estimated for the cell count and differentiation for the established emergency programme, and a minimum of 0.5 mL should be estimated for the clinical-chemical determination of the overall protein, albumin, lactate and glucose. The cerebrospinal fluid should be collected in more

than two sterile and sealable tubes with or without the addition of preservatives; the tubes should be pre-numbered, labelled with the patient information and marked with the specified time the sample was taken [1].

Next steps are centrifugation of CSF and slide preparation. The objective of the slide preparation is to have an optimum cell yield in the microscope's field of vision. All cell populations contained in the cerebrospinal fluid must be present in the slide preparation, without their proportion to one another having changed. As a result of centrifugal force, at cytologic examination sometimes cells may appear to be larger or deformed. For instance in lymphocytes, the nucleus may appear more prominent, which complicates distinguishing malign cells from normal lymphocytes [2].
Concentrating cerebrospinal fluid which is low in cells is especially significant in order to avoid missing tumour cells, especially in cases of acute myeloid (AML) and acute lymphatic leukemias (ALL) [3].

The most commonly affected extra medullary site in acute leukemias and highly aggressive lymphomas types is the central nervous system. The treatment for these patients is a challenge.

There are two types of CNS relapse: early CNS relapse and late CNS relapse (after at least 18 months of complete remission). The prognosis and life expectancy of patients who experience CNS relapse is very poor with a median of overall survival at six months and estimated overall 5 years survival rate of 0-1%. Frequently, these patients have isolated CNS relapse followed in the majority of cases by bone marrow recurrences within weeks or months. Therefore, CNS prophylaxis is an essential part of the new treatment protocols, not only because it leads to a reduced rate of CNS relapse but also reduces the bone marrow rate recurrence. It has been showed that over 50% of ALL patients without prophylactic CNS-directed treatment will develop CNS disease and that relapse rate can be reduced to approximately 10% with the use of current protocols (by introducing specific prophylaxis earlier).

The impact of the prognostic factors for ALL relapse is well known; some of them are:
- age (> 35 years old)
-high white blood cells count at diagnosis (>30.000/mm3 in ALL-B and >100.000/mm3 in ALL-T)
-increased LDH levels (>500U/L), increased β2-microglobulin levels
-CNS involvement at diagnosis
-cytogenetic aberrations: t(9;22), t(4;11), hyperdiploid karyotype
-mature B-cells phenotype

Researchers from M.D. Anderson Cancer Center were able to show that patients with one of the following: increased LDH, increased β2-microglobulin, high leukemia cells proliferation had 13% risk to develop CNS disease at 1 year, whilst the presences of two or more factors increased the risk to more than 20% [4]. Among all these factors, the identifying more than 5 leukemia cells/µl in the CSF was found to be the most important one.

In AML cases, the CNS involvement is very uncommon, therefore routine evaluation is not recommended. The incidence, once estimated at 16 % prior to the use of high doses of cytarabine which can penetrate into the CNS, has been decreasing ever since [5]. The risk factors that had been associated with CNS relapse in AML are:
-FAB subtype: acute myelomonocytic leukemia (AML4-FAB), acute monoblastic leukemia (AML5a-FAB), acute monocytic leukemia (AML5b-FAB)
-relapsed acute promyelocytic leukemia (APL) with PML/RARA
-hyperleucocytosis at diagnosis >100.000/mm3
-cytogenetic abnormalities: inv(16), chromosome 11 abnormalities, complex karyotype
-CD56 expression on the blasts cells surface

As for aggressive lymphomas CNS relapse is common in Burkitt lymphoma (30–50%), less common in mantle cell lymphoma (4–23%) in diffuse large B cell lymphoma (DLBCL) (2–10%) and in indolent lymphoma CNS relapse is 0–4% [6].

Without CNS-directed prophylaxis, patients develop CNS relapse in the first 6 to 10 months from the diagnosis with a median survival no higher than 6 months. CNS relapse affects more often the leptomeningeal system and less the parenchyma.

The major approaches regarding the treatment are:
-intrathecal triple therapy with 15mg methotrexate, 30-40mg cytarabine and 4mg dexamethasone [7]
-liposomal cytarabine (DepoCyte): 50mg every 2 weeks, frequently associated with chemical

meningitis; with a half-time in the CSF of 84 hours; it's usually administrated with dexamethasone orally 4mg /twice daily for 5 days ; intrathecal DepoCyte is composed of cytarabine held within aqueous chambers and encapsulated by lipid bi-layers; These particles were not visible on cytospin preparations, either when CSF was spun alone or when it was resuspended in albumin, suggesting that the particles were too fragile to remain intact during cytospin preparation (fig. 45-48) [8].
-high doses chemotherapy combination 1- 5g/m2 methotrexate and cytarabine 2-3g/m2 [7].
-cranial irradiation (12 to 18Gy) is a very effective form of CNS-directed therapy but its efficacy is offset by all the acute and long-term toxicities. Acute: mucositis, myelosuppresion and esophagitis. Long-term: secondary neoplasm, neurotoxicity, endocrinophathy [9].
-TBI - total body irradiation for allogeneic bone marrow transplantation used in younger patients but with lots of complications.
-Thiotepa – an alkylating agent for systemic use and that can also be administered into the CSF.
The diagnosis of central nervous system relapse was confirmed by lumbar puncture and cytological examination of the cerebrospinal fluid. All images are from our collection (from the Hematology Clinic, Fundeni Clinical Institute).

Acute myelomonocytic leukemia (AML4-FAB), figure 1-4: slides from concentrated cerebrospinal fluid, May Grumwald-Giemsa stain, x1000: myeloblasts, monoblasts, promonocytes.

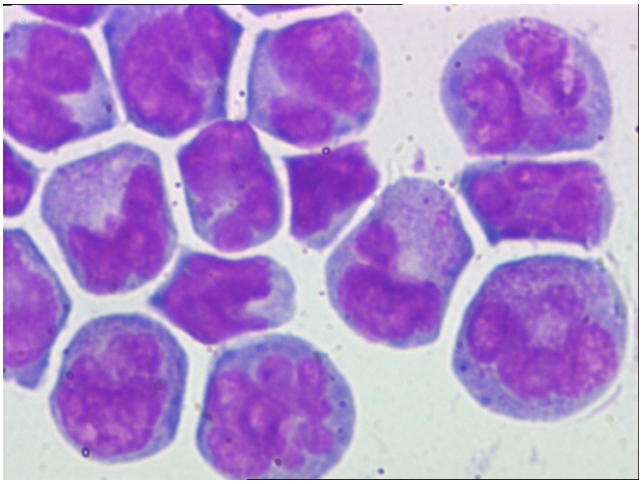
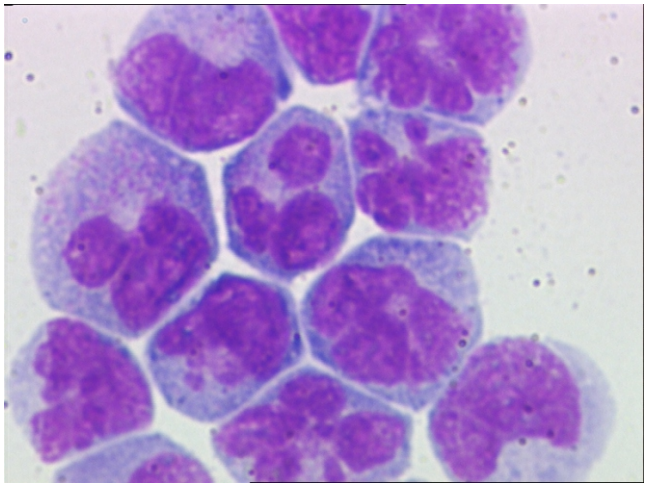


Figure 1.



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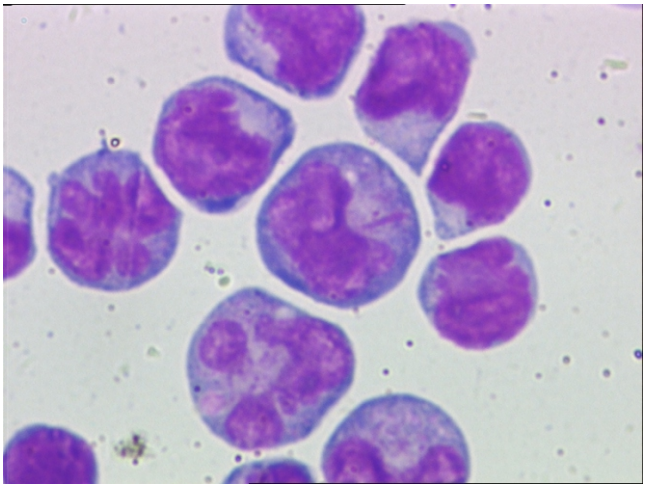

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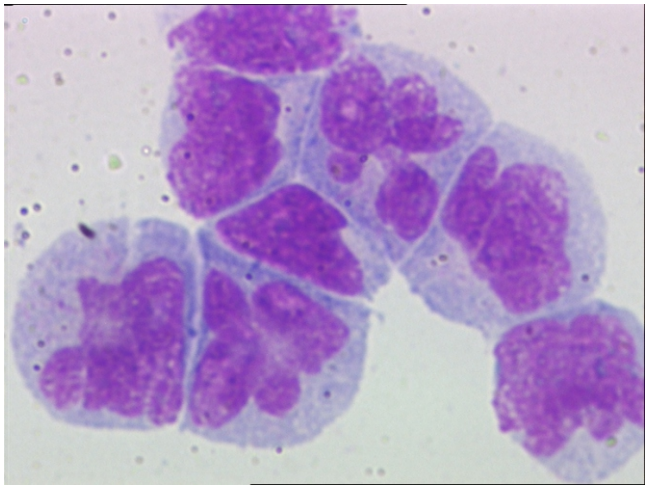
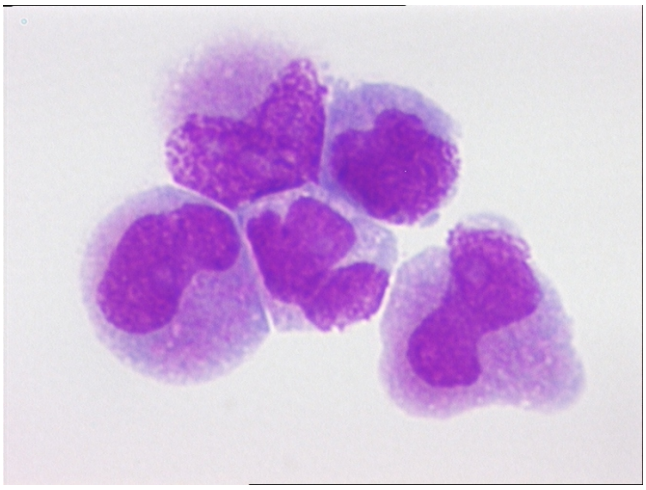


Figure 4.

Acute promyelocytic leukemia (APL), figure 5-17: slides from concentrated cerebrospinal fluid, May Grumwald-Giemsa stain, x1000: promyelocytes.



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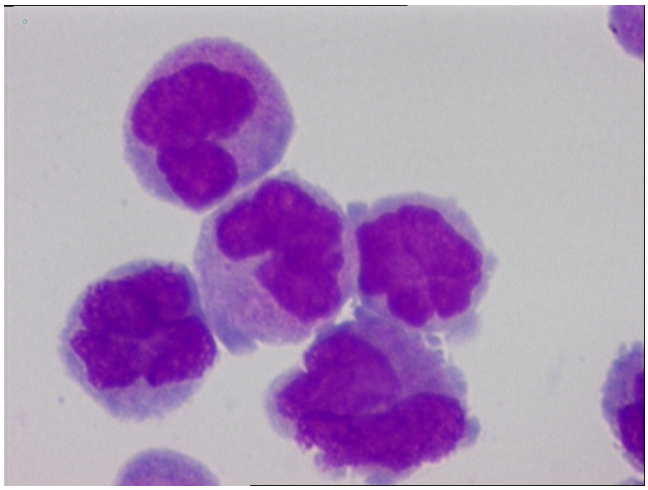
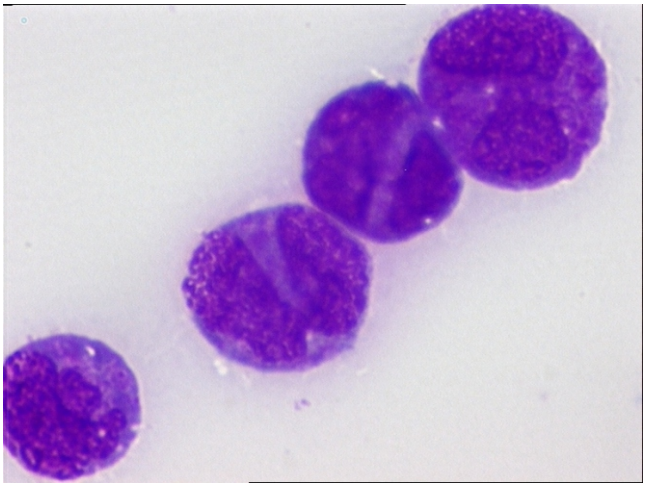


Figure 6.



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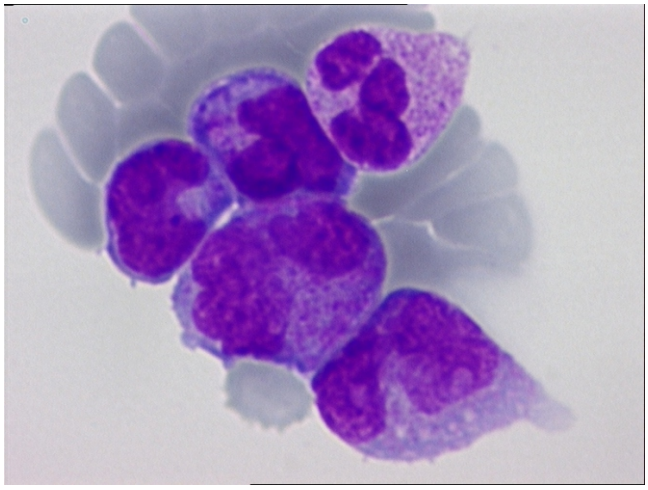

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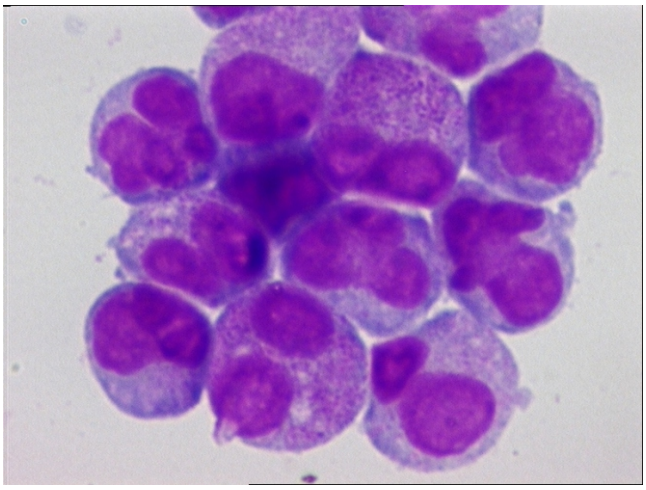

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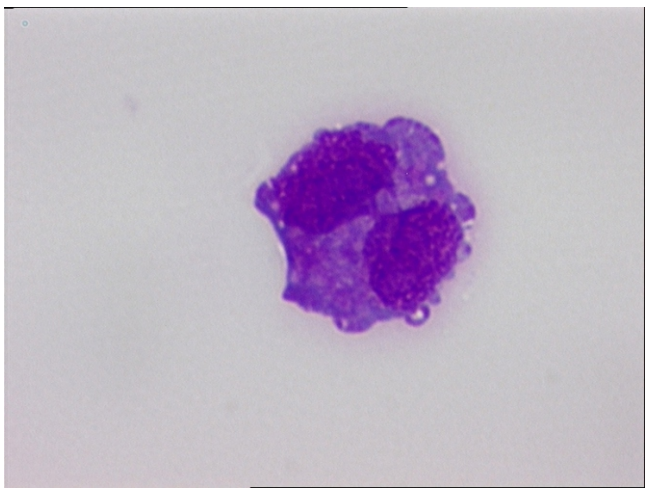

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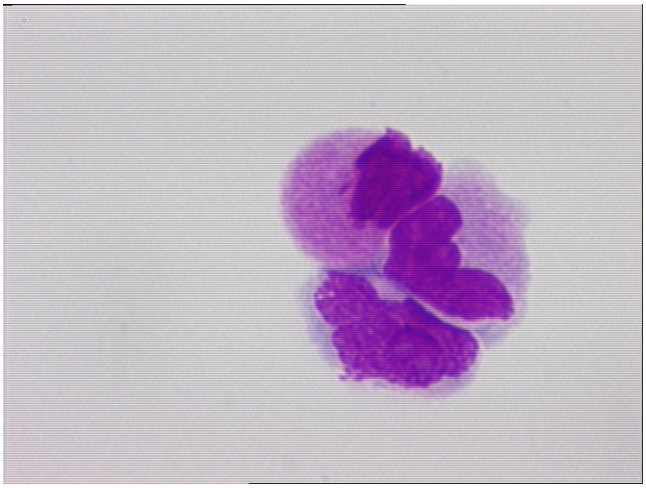

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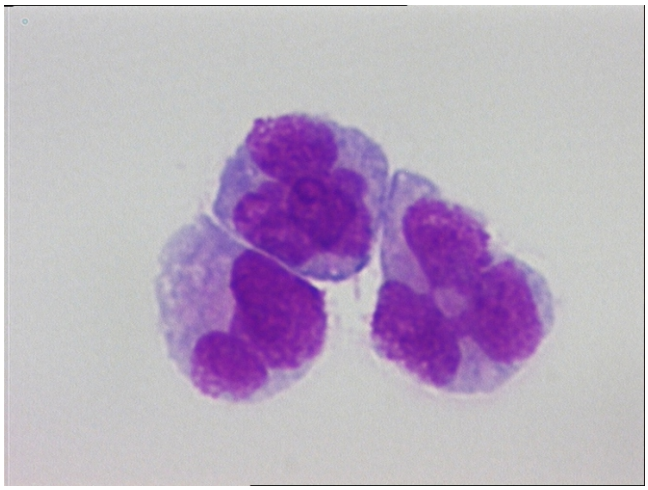

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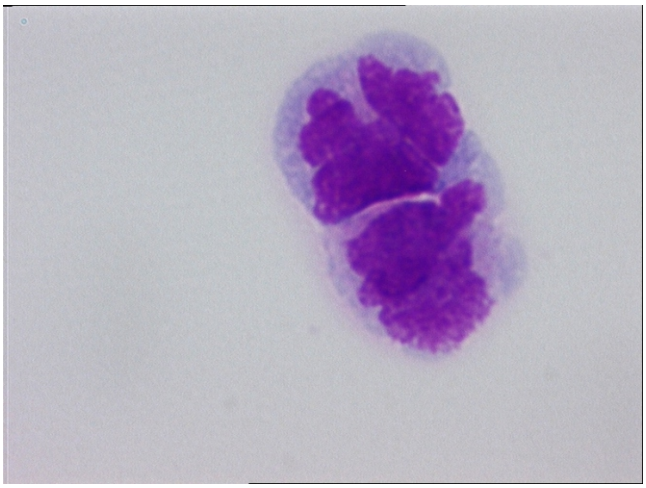

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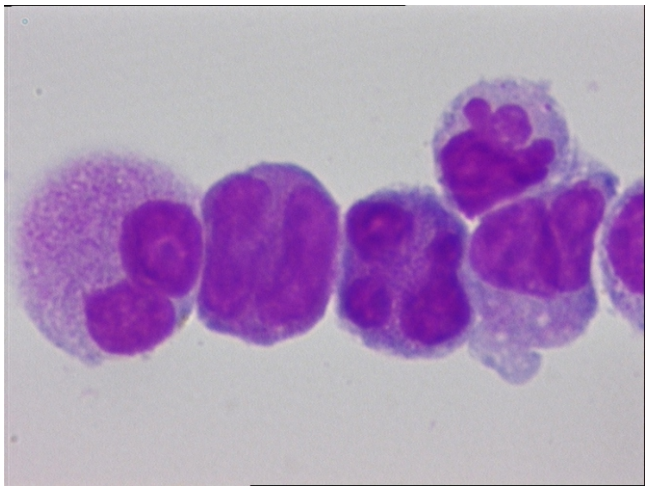

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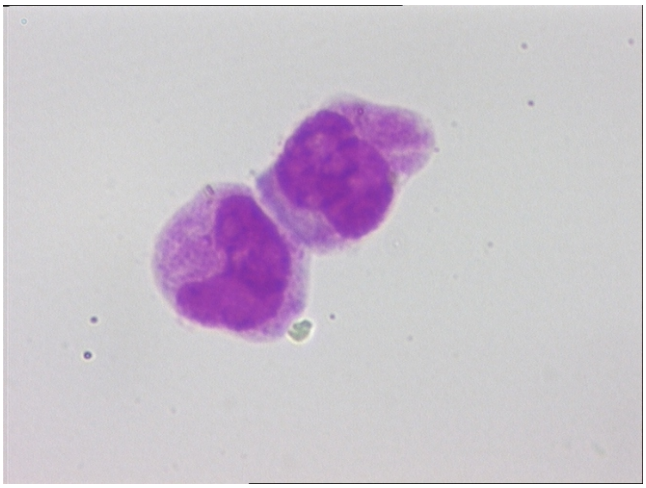

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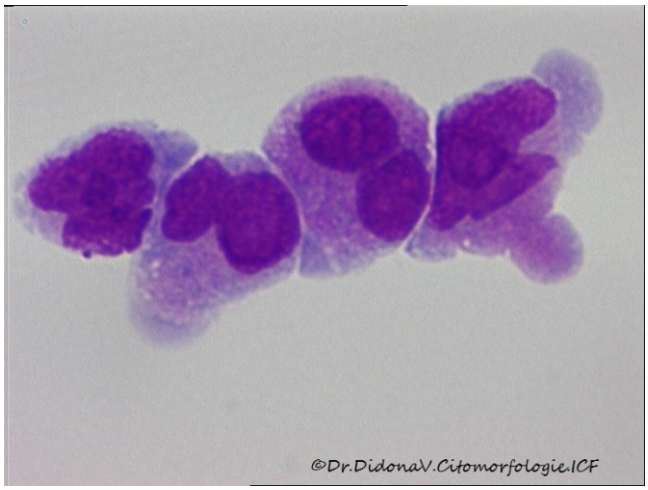
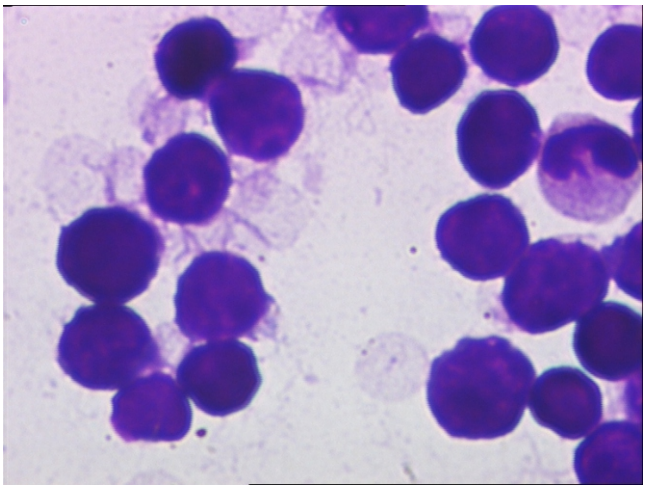


Figure 16.

Acute Lymphoid Leukemia, figure 17-22: slides from concentrated cerebrospinal fluid, May Grumwald-Giemsa stain, x1000: lymphoblasts.



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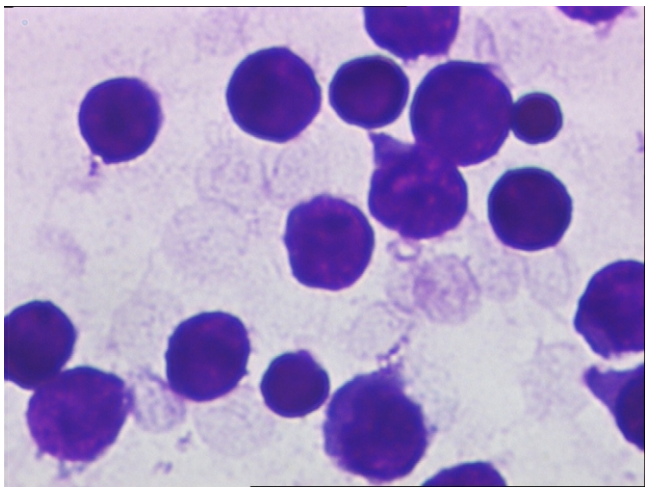

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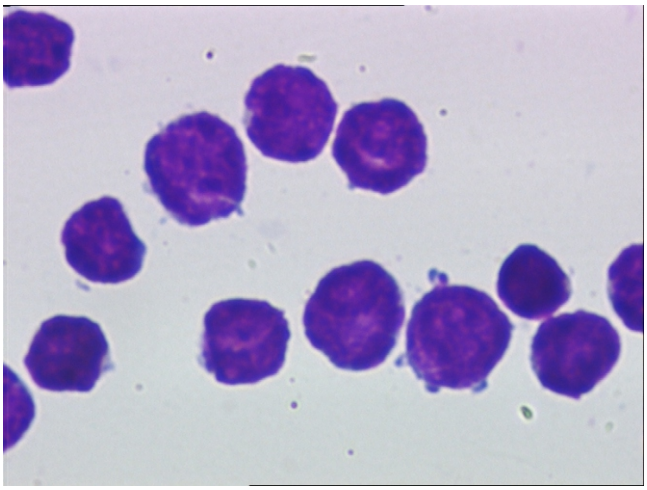

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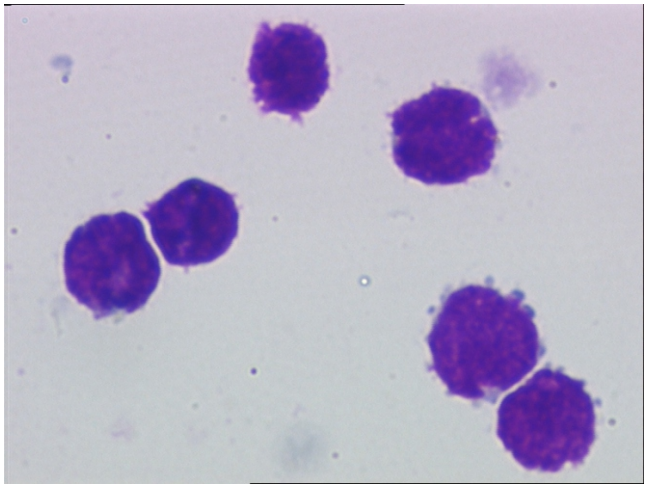

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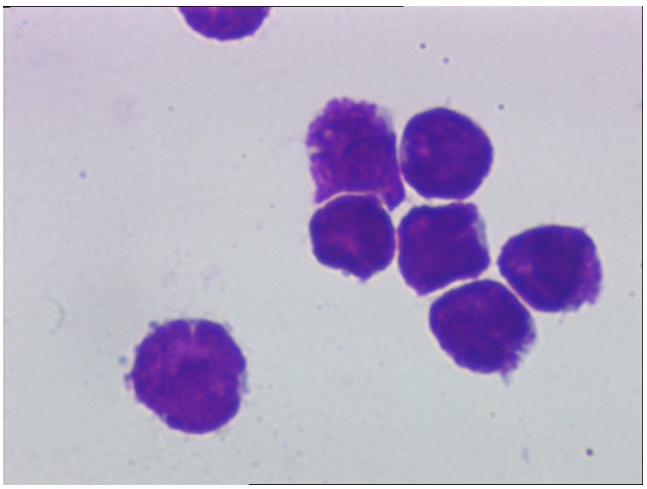

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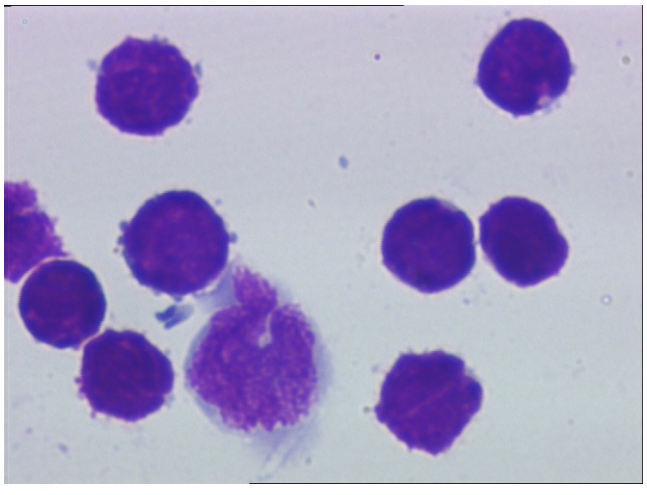


Figure 22.

Malignant Lymphomas, figure 23-44: slides from concentrated cerebrospinal fluid, May Grumwald-Giemsa stain. Lymphoid elements.

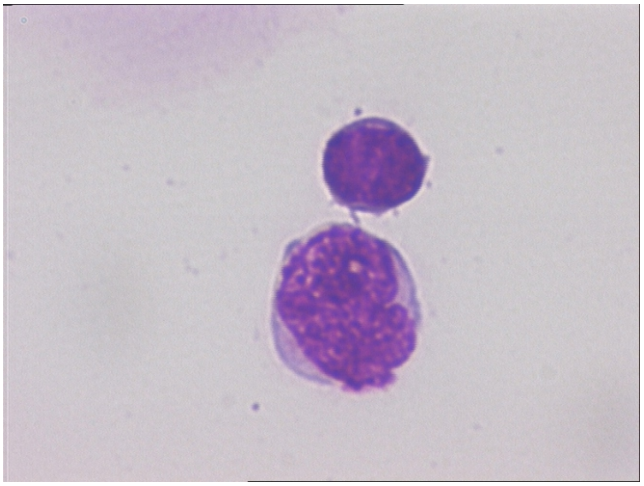
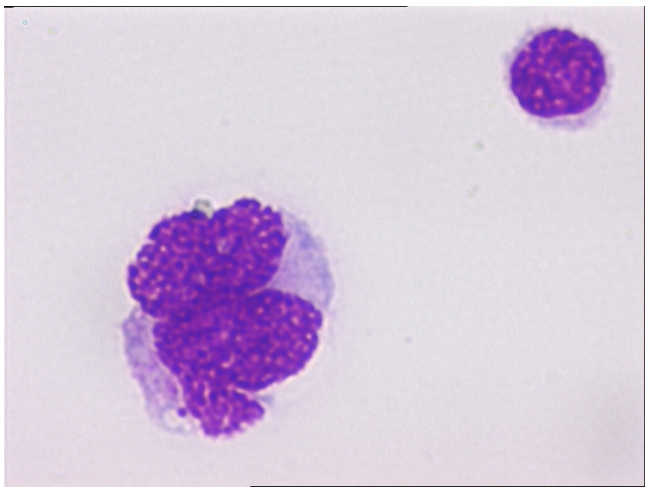


Figure 23. Diffuse Large B-Cell Lymphoma, 1000x.



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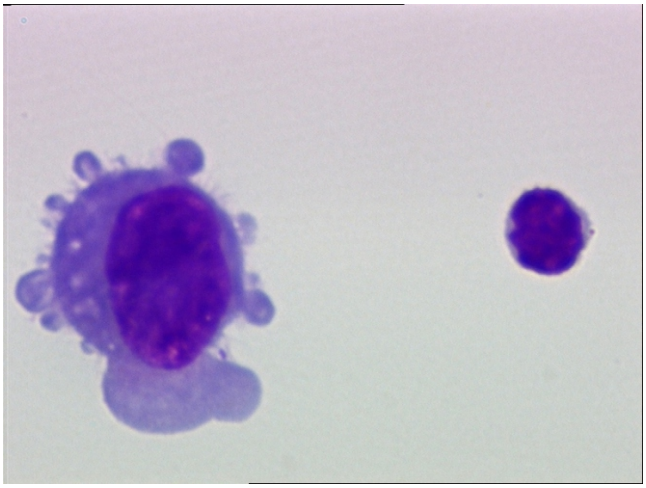

Figure 25. Diffuse Large B-Cell Lymphoma, 1000x.

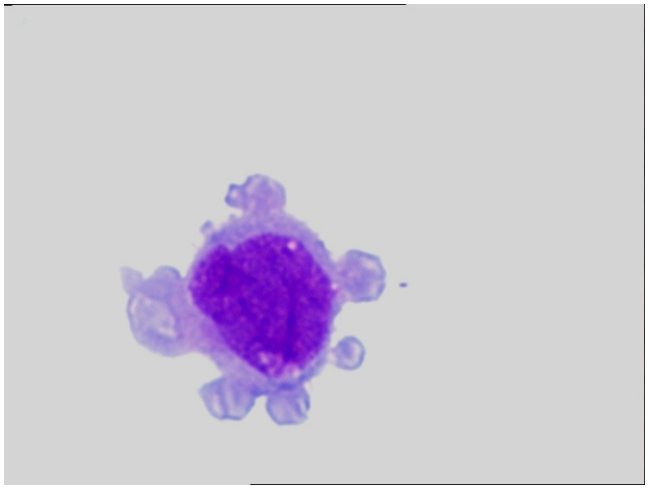

Figure 26. Diffuse Large B-Cell Lymphoma, 1000x.

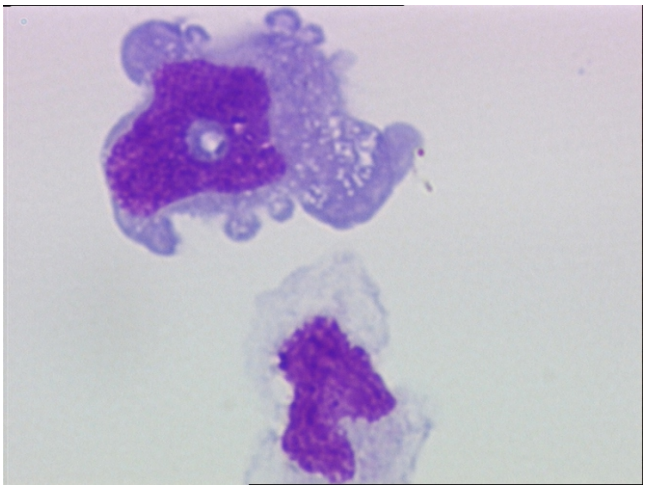

Figure 27. Diffuse Large B-Cell Lymphoma, 1000x.

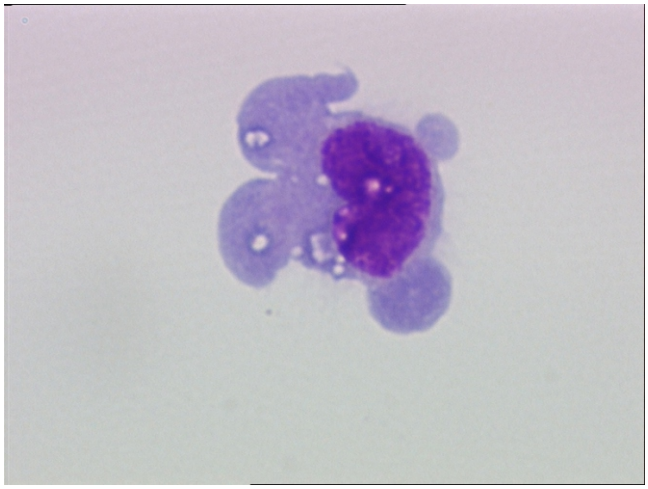

Figure 28. Diffuse Large B-Cell Lymphoma, 1000x.

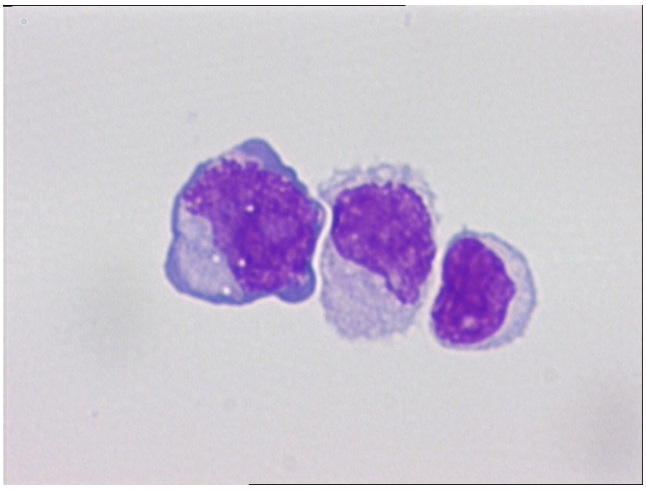

Figure 29. Malignant Lymphoma, 1000x.

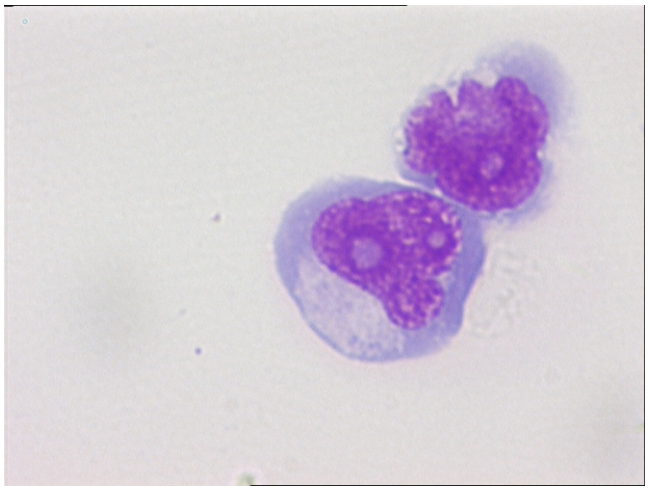

Figure 30. Malignant Lymphoma, 1000x.

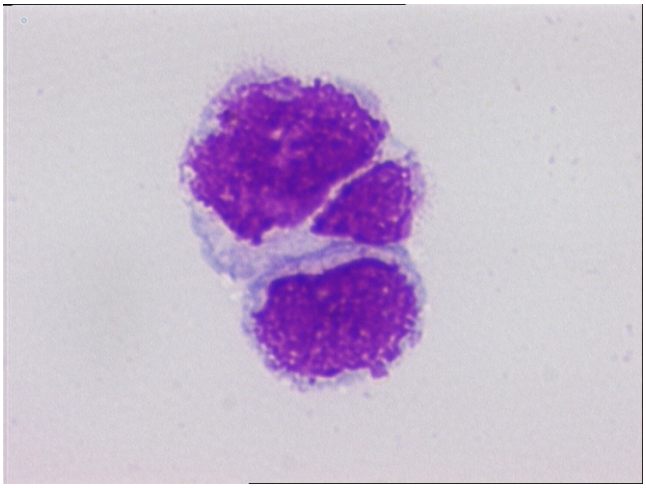

Figure 31. Malignant Lymphoma, 1000x.

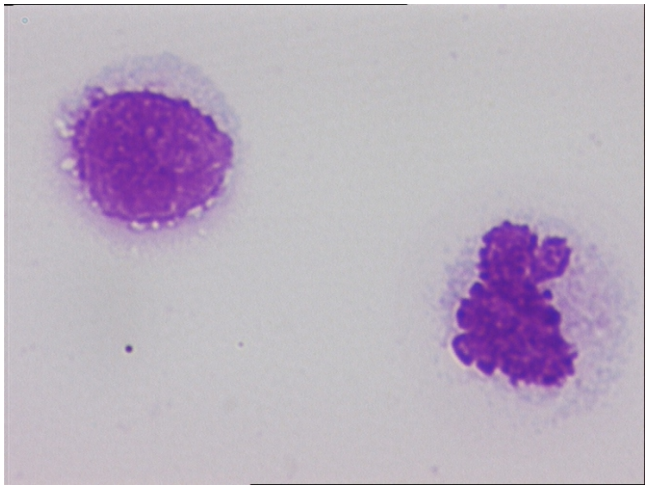

Figure 32. Malignant Lymphoma, 1000x.

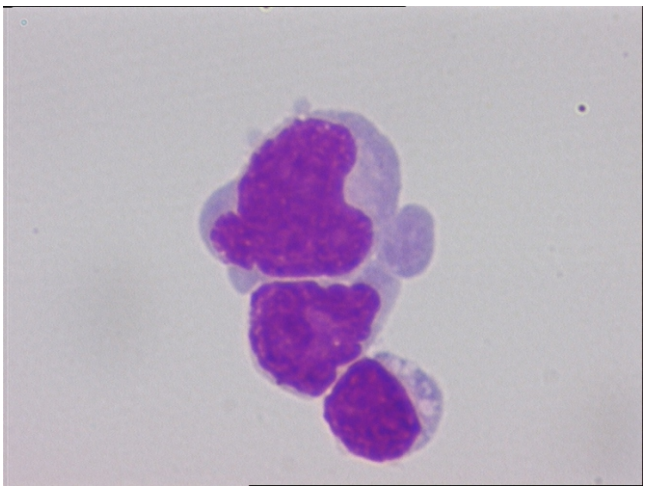

Figura 33. Burkitt lymphoma. 1000x

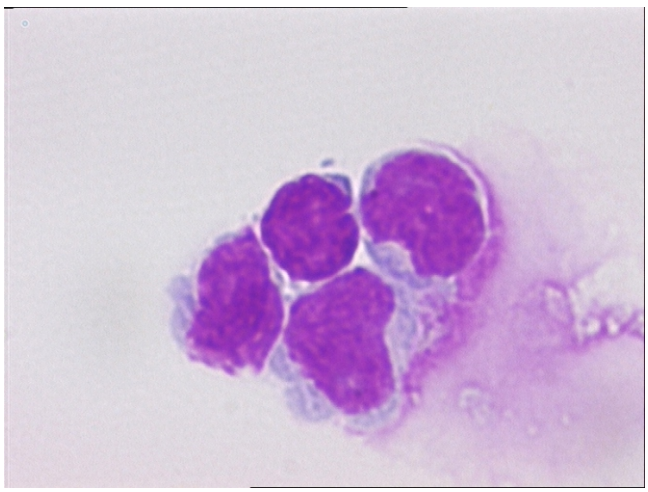

Figura 34. Burkitt lymphoma. 1000x

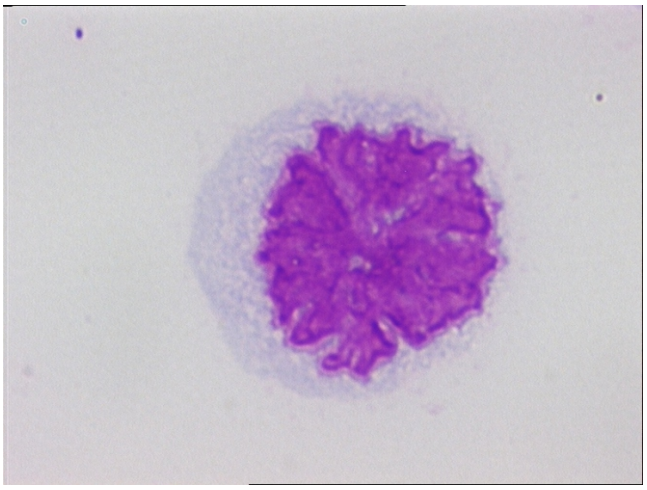

Figure 35. Burkitt lymphoma. 1000x.

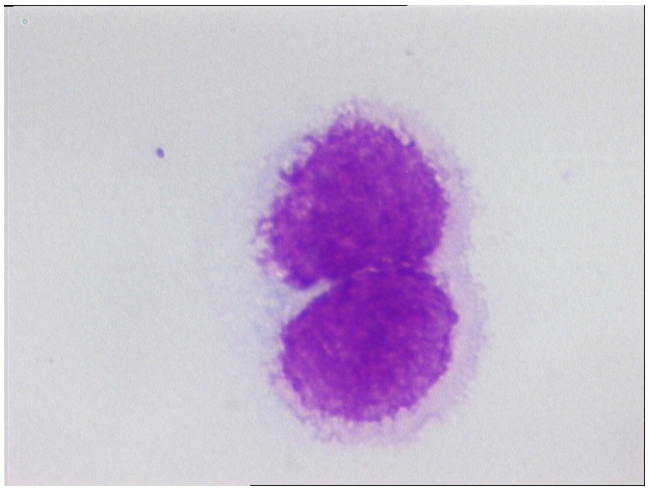

Figure 36. Burkitt lymphoma. 1000x.

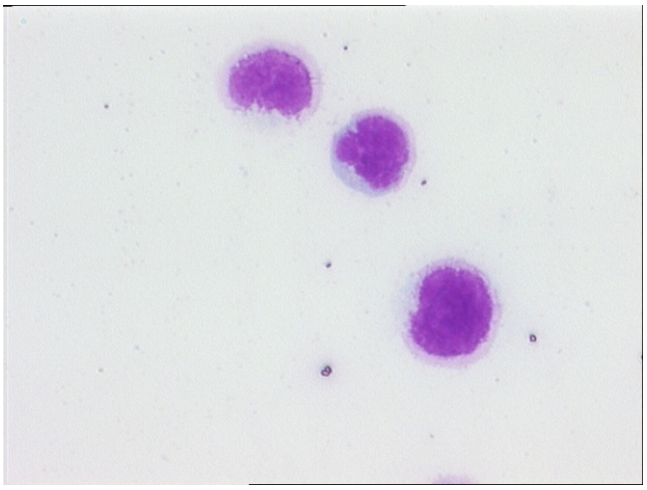

Figure 37. Burkitt lymphoma. 400x

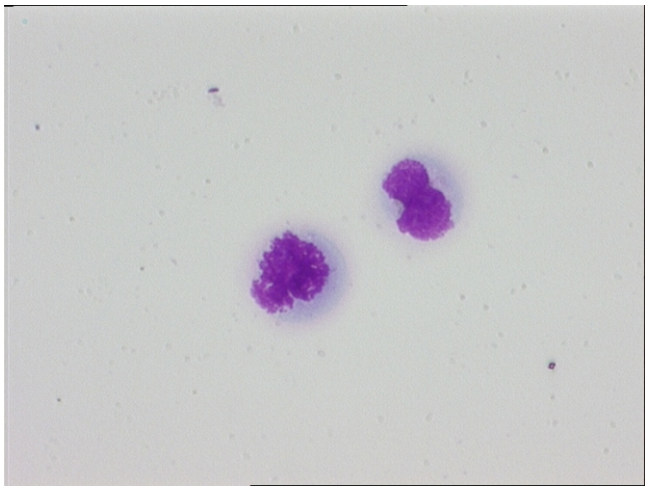

Figure 38. Burkitt lymphoma. 400x

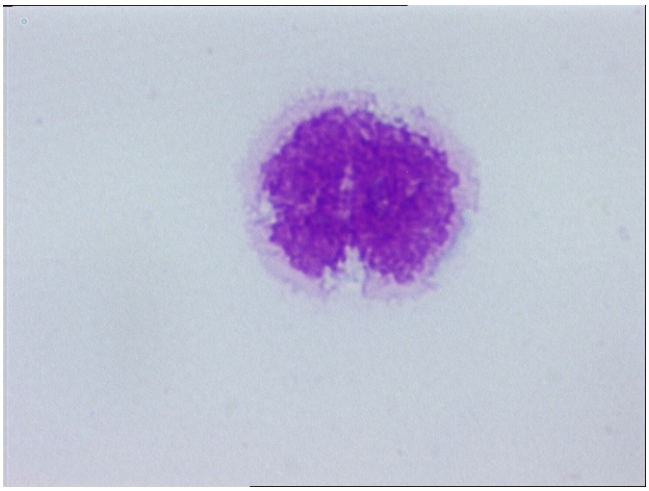

Figure 39. Burkitt lymphoma. 400x

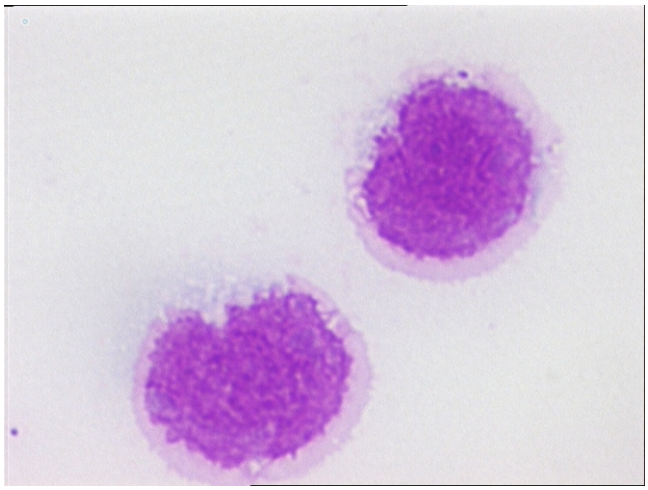

Figure 40. Burkitt lymphoma. 1000x.

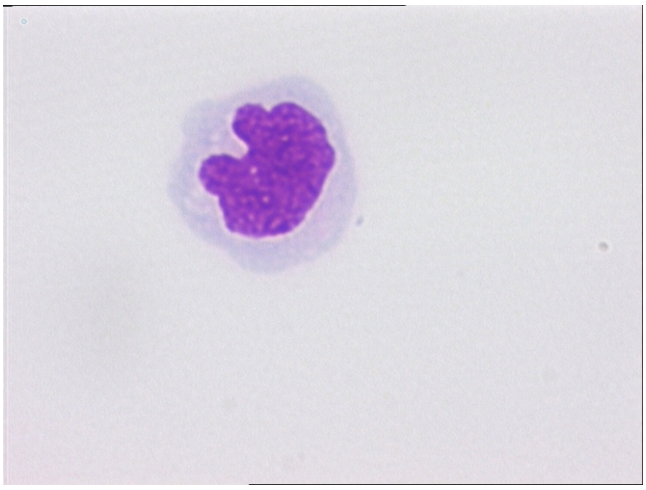

Figure 41. Anaplastic lymphoma, 1000x.

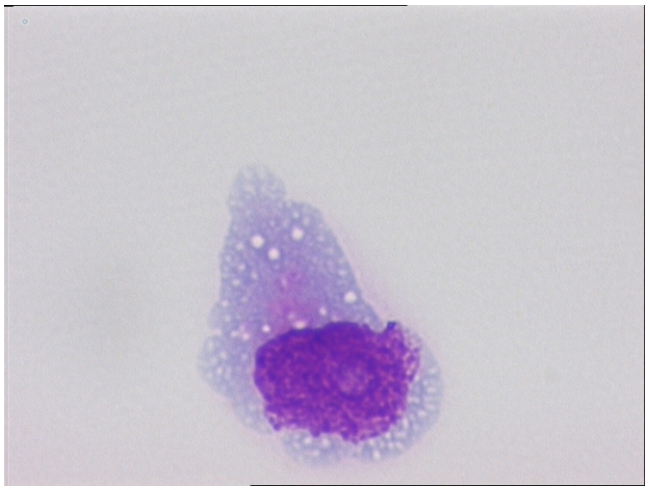

Figure 42 Anaplastic lymphoma, 1000x.

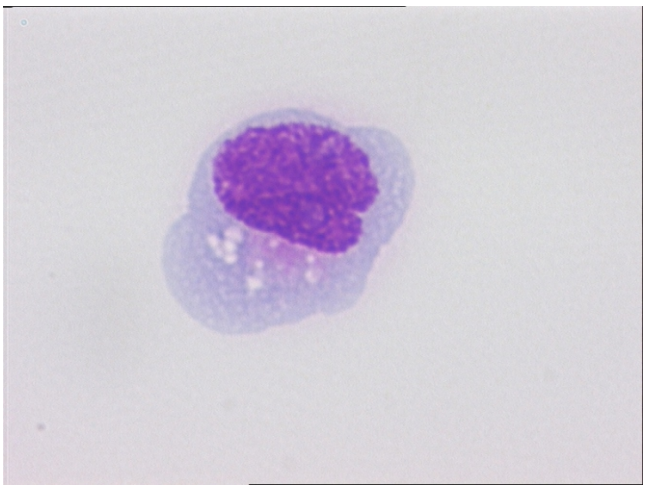

Figure 43. Anaplastic lymphoma, 1000x.

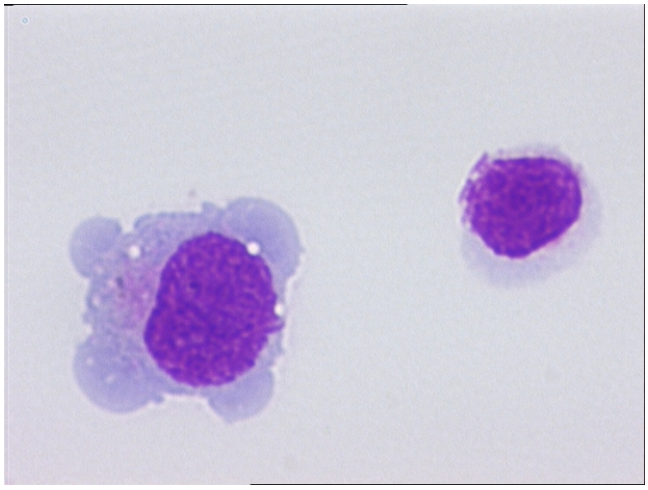

Figure 44. Anaplastic lymphoma, 1000x.

Figure 45-48: cerebrospinal fluid in Nageotte counting chamber – DepoCyte treatment.

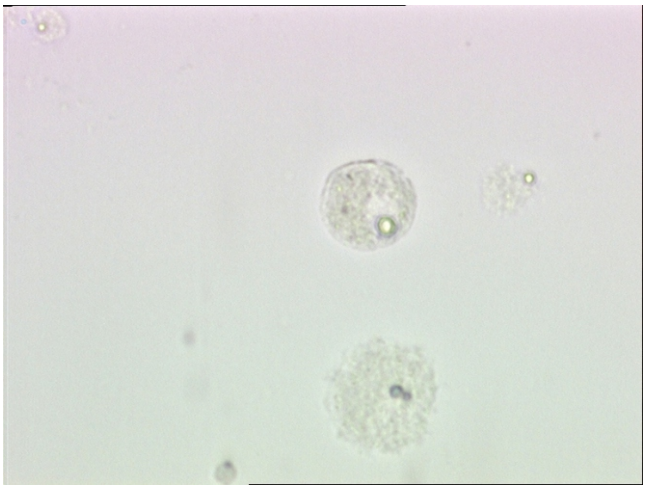

Figure 45

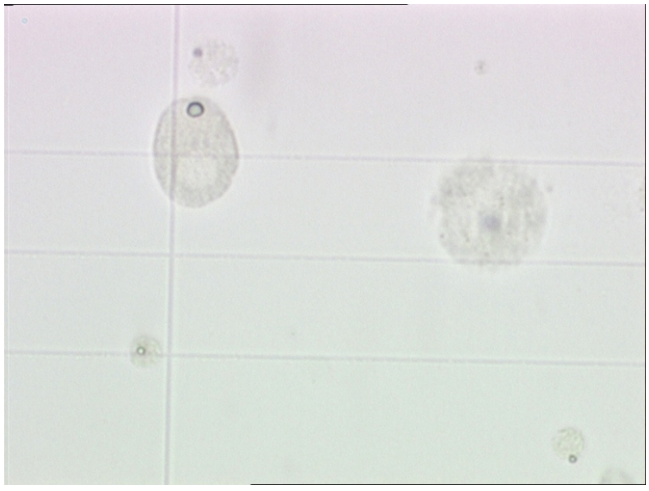

Figure 46

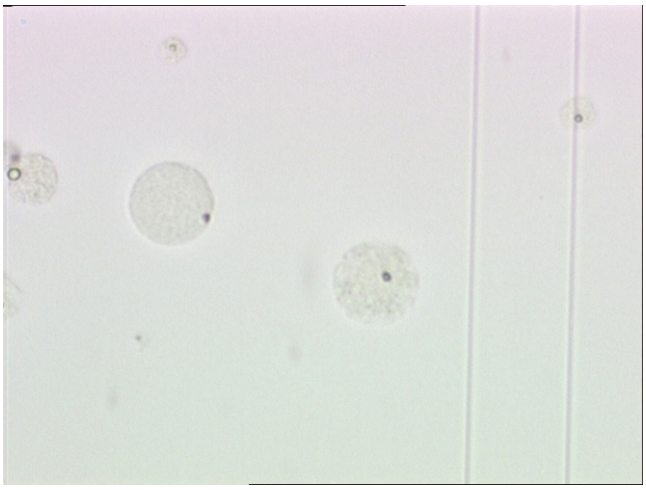

Figure 47

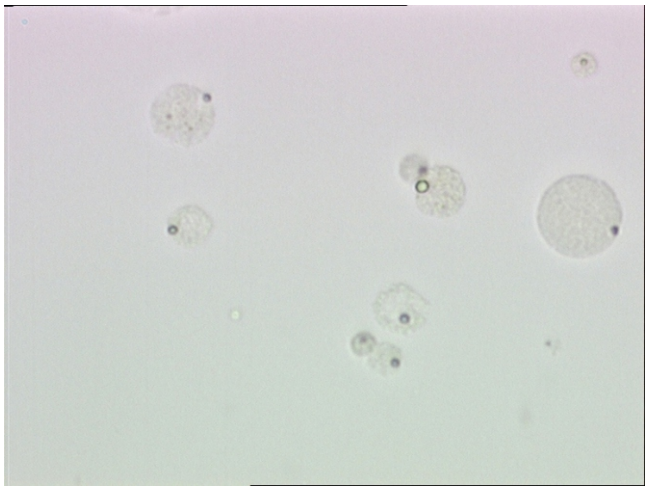

Figure 48

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Systemic Mastocytosis associated Acute Myeloblastic Leukemia with t(8;21): Case report

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Abstract

Systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) is a rare and advanced form of systemic mastocytosis. Patients with SM-AHN are most often diagnosed with myeloid malignancies – most frequent myelodysplastic syndrome and myeloproliferative neoplasm and represent a challenge to manage, these patients requiring the parallel treatment of both SM and the AHN. We present the case of a 69 year-old woman diagnosed at first with systemic mastocytosis and unclassifiable myeloproliferative neoplasm based on the presence of multifocal dense infiltrates of mast cells on bone marrow (BM) biopsy and the KIT D816V mutation, coupled with high white blood cell count (90 000/μL) with general elements of myeloid proliferation on BM. After the first evaluation the patients was treated with weekly subcutaneous cladribine administrations. After 3 administrations the patients was admitted to the emergency room with fever (38.3°C), generalized bone pain. The laboratory evaluation revealed a complete blood count with 25 000/μL WBC, a hemoglobin level of 8.7 g/dL, and 40 000/μL platelet count, the peripheral blood smear (PBS) revealed a blast count of 34%. The patient was reevaluated with BM aspiration with morphologic evaluation describing 7% myeloblasts with Auer rods, flow cytometry evaluation describing 13% myeloid precursor cells – myeloblasts without maturation. The patient was diagnosed with acute myeloblastic leukemia M1 FAB – due to the presence of circulation myeloblasts 30%.

Due to the patient's age and the low performance status she was considered non-fit for standard 7+3 chemotherapy and treatment was started with decitabine, the patient underwent 1 cycle. Death occurred 10 days after admittance with subdural hematomas and cerebral edema. On cytogenetic evaluation the patients was retrospectively diagnosed with translocation t(8;21)(q22;q22) and trisomy of chromosomes 6 and 15. On molecular testing the RUNX1-RUNX1T1 fusion transcript was detected. The final diagnosis was SM-AHN – acute myeloblastic leukemia with t(8;21)(q22;q22.1).

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Introduction

Systemic mastocytosis is a heterogeneous group of diseases characterized by the accumulation of mast cells in extracutaneous tissues and patients are classified into five clinical variants according to the WHO 2016 classification1. Of these variants, SM-AHN is a rare and heterogeneous group. These patients can develop both myeloid and lymphoid malignancies2. In cases with myeloid neoplasms the most frequent associated are myeloproliferative and myelodysplastic syndromes, but these patients can also present acute myeloblastic leukemia (AML). The general consensus is that for the management of patients with SM-AHN the goal is to treat the two diseases in parallel – the treatment of advanced SM and the treatment of the associated hematologic neoplasm3, 4. In cases with associated AML the most frequent recurrent mutation is the translocation t(8;21)(q22;q22.1)5–7.

Case presentation

A 69 year-old women, with a history of chronic hepatic virus B infection, osteoporosis, lumbar disc disease, was addressed to a hematologist in march 2016 for malaise, loss of appetite, weight loss of around 25 kg in 8 months, generalized bone pain, and occasional bouts of resting dyspnea. The physical examination revealed: malaise, generalized bone pain, paleness, no skin lesions were observed, mild hepatomegaly and splenomegaly +2 cm from costal margin. The CBC revealed leukocytosis WBC 90 000/μL with 85% neutrophils, moderate normocytic normochromic anemia Hgb 9.5 g/dL, mild thrombocytopenia PLT 75 000/μL. BM biopsy was performed which revealed a hypercellular BM with proliferation and maturation of myeloid progenitors, and multifocal dense infiltrates of mast cells with a total percent of mast cells of 10%, with expression of CD25 on immunohistochemical stain. Next the patient was tested for KIT activating mutation and was found positive for the KIT D816V mutation. After the first evaluation the diagnosis was SM with unclassifiable myeloproliferative neoplasm and received symptomatic treatment. In august 2016 due to the aggravation of the clinical signs treatment was started for SM with weekly subcutaneous cladribrine administration. After 3 weekly administrations the patients was admitted to the emergency room with high fever (38.3°C), generalized bone pain. The physical examination revealed malaise and fatigue, aggravated bone pain, cutaneous pallor, without hemorrhagic or other skin lesions, persistent mild hepatomegaly and splenomegaly +2 cm from costal margin. The ECOG performance status at admittance was evaluated at 3. The laboratory evaluation revealed a complete blood count with 25 000/μL WBC, mild anemia Hgb 8.7 g/dL, and moderate thrombocytopenia 40 000/μL PLT, the PBS revealed a blast count of 34%. The patient was reevaluated with BM aspiration with morphologic evaluation describing 7% myeloblasts with Auer rods. Flow cytometry evaluation described 13% myeloid precursor cells with the following immunophenotypic characteristics: CD45 low SSC low CD33+ CD13+ CD14- CD64+ CD300e- CD35- CD36- CD38+ CD203c- CD105- CD34+ CD117+ CD11b- CD25- CD56- HLA-DR+ cMPO-/+ cCD79a- cCD3- CD3- CD7- CD2- CD10- CD19- CD9-, suggestive for myeloblasts without maturation. Samples for cytogenetic and molecular studies were also harvested at this time. The patient was diagnosed with acute myeloblastic leukemia M1 FAB – due to the presence of circulation myeloblasts 34%. Due to the patient's age and the low performance status she was considered non-fit for standard 7+3 chemotherapy and treatment was started with decitabine, the patient underwent 1 cycle. Despite treatment for AML the patients general state deteriorated: persistent fever >38°C, aggravated generalized algic syndrome. The CBC and PBS evaluation after decitabine revealed increasing leucocyte count >100 000/μL with a blast count of 52%, an Hgb level of 8.7 g/dL, PLT count 35 000/μL. The patient was started on cytoreductive therapy with 5-hydroxyurea. Shortly after the patient status deteriorates with hemorrhagic complication, a cerebral-CT scan revealed subdural hematomas and generalized cerebral edema; the patient was admitted to the intensive care unit (ICU). Death occurred shortly after ICU-admittance, 10 days after ER-admittance in early September 2016.

On cytogenetic evaluation the patients was retrospectively diagnosed with translocation t(8;21)(q22;q22) and trisomy of chromosomes 6 and 15 (Figure 1). On molecular testing the RUNX1-RUNX1T1 fusion transcript was detected. The final diagnosis was SM-AHN – acute myeloblastic leukemia with t(8;21)(q22;q22.1).

Discussions

In the case presented here the diagnosis of SM was based on the presence of mastocyte aggregates on BM (1 major) and the presence of the KIT D816V mutation (1 minor) according to the World Health Organization classification1. Regarding the hematological associated neoplasm at first the patient was diagnosed with unclassifiable myeloproliferative neoplasm which later evolved into AML with t(8;21)(q22;q22.1). Unlike the previously reported cases and case series of SM with AML with t(8;21)(q22;q22.1) in which the diagnosis of SM was followed after the AML diagnosis the patient was first diagnosed with SM and after with AML5–8.

Regarding the treatment options for SM-AHN the current consensus for the treatment is that each

disease should be treated in parallel3,4. For advanced SM with KIT D816V mutation the treatment options currently recommended are interferon alfa, cladribine and midostaurin, of these the only drug available was cladribine. As for AML treatment as stated above given the patient's advanced age and low performance status did not permit the administration of standard 7+3 chemotherapy and treatment with decitabine was opted.

Conclusions

We presented a rare case of SM associated with AML with t(8;21). Despite the early recognition of the disease complex, and the best possible treatment accorded adapted to the patient's advanced age and low performance status, due to the aggressive nature of SM-AHN the patient deceased after only 10 days since diagnosis of AML. This case further illustrates that although AML with t(8;21) represent one of the favorable prognostic AML with recurrent genetic mutation, the association with SM in turn offers a dismal prognosis.

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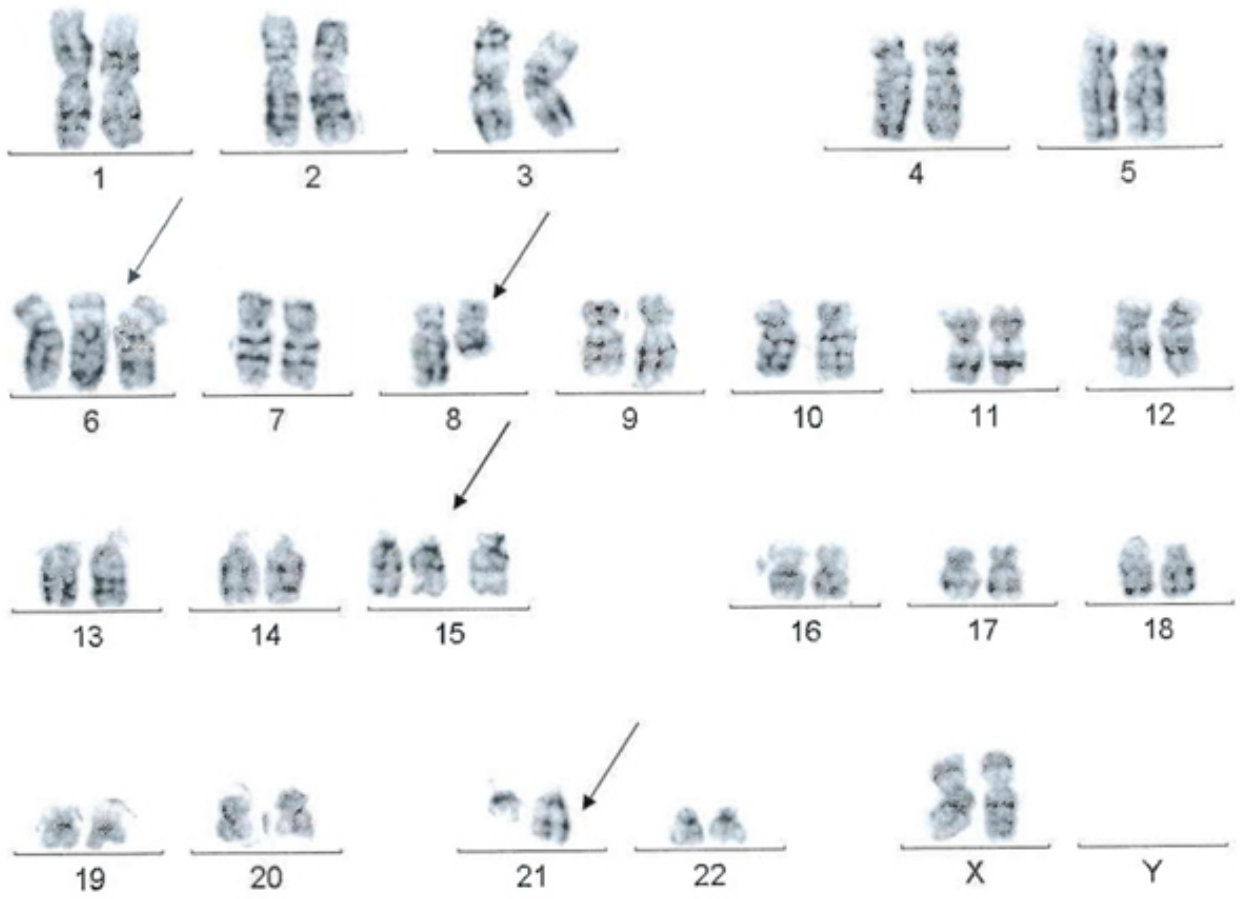

Figure 1 – Patient's karyotype presenting translocation t(8;21)(q22;q22) and trisomy of chromosomes 6 and 15.

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Myeloid Chronic Leukemia patient with QT interval prolongation after Nilotinib treatment

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Abstract

One dangerous adverse effects of Nilotinib is QT prolongation syndrome, which can produce torsades des pointes and a fatal outcome. When a patient treated with Nilotinib develops QT prolongation syndrome, it is important to check for another cause of this ECG change: serum electrolytes changes, other diseases, concomitant medications with QT prolongation potential. For these cases, the theoretical part of this paper includes a practical protocol of QT prolongation syndrome produced by Nilotinib.

We report a clinical case of a 73 years old male with Chronic Myeloid Leukemia- chronic phase treated with Imatinib. The patient had a "warning response" at 8 months after starting the treatment. After that, the treatment was changed on second generation tyrosine kinase inhibitors, Nilotinib, which produced QT prolongation syndrome, after a week of treatment. We reduced the dose finally at 2x150 mg/day and the patient developed a deep molecular response, maintained for 17 months. Unfortunately, the patient died because of another cause.

In conclusion, this case report highlights the issue of changing the tyrosine kinase inhibitors, the importance of ECG monitoring during the Nilotinib treatment and the management of QT prolongation syndrome.

Keywords*: QT prolongation syndrome, Nilotinib, Chronic Myeloid Leukemia*

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Introduction

Survival in Chronic Myeloid Leukemia (CML) has significantly improved since 2001, when tyrosine kinase inhibitors (TKI) were introduced. This drugs minimized the impact of known prognostic factors and produced a revolutionary change in the management of CML patients.

TKIs share a number of common adverse effects (AE), including neutropenia and thrombocytopenia. Cardiotoxicities of the TKIs have become a modern clinical concern. (1, 2)

Nilotinib may produce cardiac disorders like angina pectoris, arrhythmia (including atrioventricular block, tachycardia, atrial fibrillation, ventricular extrasystoles, bradycardia), electrocardiogram QT prolonged, palpitations, myocardial infarction.

It is well known that Nilotinib may prolong (in a concentration-dependent manner) cardiac ventricular repolarization which is measured by the QT interval on ECG. Cardiologists use heart rate-corrected QT interval, by Bazett's formula (QTcB) or by Fridericia's formula (QTcF). Normal ranges are: QT normal = 350-440 msec, "borderline" QT prolongation = 440-480 msec, QT prolongation>480 msec. (1, 3, 7)

In the Phase III study, in patients treated with 2x 300 mg Nilotinib/day, the change from baseline QTcF interval was 6 msec. No patient had a QTcF >480 msec. No episodes of torsade de pointes were observed. (1, 3, 4, 5)

QT interval prolongation may occur when Nilotinib is associated with strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT. Changes in serum electrolytes like hypokalemia and hypomagnesaemia may enhance this effect. Prolongation of the QT interval may expose patients to the risk of fatal outcome by producing torsades des pointes, a ventricular tachycardia

called which can result in syncope, seizures, and/or death. (4, 6)

Nilotinib should be used with caution in patients who have or who are at significant risk of developing prolongation of QTc: a. congenital long QT prolongation (the Romano-Ward syndrome, Jervell and Lange-Nielsen (JLN) syndrome, which is associated with congenital deafness, uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia, b. taking anti-arrhythmic medicinal products or other substances that lead to QT prolongation (amiodarone, disopyramide, procainamide, quinidine, sotalol chloroquine, clarithromycin, haloperidol, methadone and moxifloxacin). (3, 4, 7)

An interesting study was done on a group of Imatinib-resistant patients with CML, treated with Nilotinib which caused a maximum mean QT change of 10 ms from baseline. In 2.1% of the patients treated with Nilotinib, QT increase was over 60 msec and in less 1% of patients QT was over 500 msec. Sudden deaths were reported in 0.6% of patients in a clinical study, and at a similar frequency in an expanded access study. The early occurrences of some of these deaths related to the start of Nilotinib treatment suggest that ventricular repolarization may have contributed to their occurrence. (1)

A practical protocol for management of QT prolongation syndrome caused by Nilotinib treatment was published by Xu and col: When QTc >480 msec:

1) Withhold therapy, correct serum potassium and magnesium levels if below normal, and review concomitant medication;
2) Resume at prior dose in 2 weeks if QTc returns to <450 msec and <20 msec of baseline
3) Reduce dose to 400 mg/day if QTc 450-480 msec after 2 weeks;
4) Discontinue if QTc returns to >480 msec after dose reduction;
5) Repeat ECG assessment approx. 7 days after any dose adjustment (1)

Case report

A 73 years old male with a medical history of arterial hypertension (2nd degree), aortic stenosis, mitral insufficiency, hypercholesterolemia, was referred to Oncological Institute Cluj, Hematology Department in march 2015. His physical complains were asthenia, adynamia and fatigue. Physical examination: splenomegaly at 3 centimeters under the costal margin. The complete blood count showed a hiperleukocytosis (273,000/microL), normal erythrocyte count, normal hemoglobin and thrombocytosis (881,000/microL). Peripheral blood smear: left shift, 10% of basophils. BCR-ABL/ABL=100% (real-time PCR, peripheral blood, p210). The diagnosis was Chronic myeloid leukemia- chronic phase, high risk Sokal, high risk Hasford, low risk EUTOS. At the debut, renal function was impaired due to hyperuricemia and uric nephropathy. The patient developed a spontaneous tumor lysis syndrome, too.

We administrated the patient Hydroxyurea (doses: 2-4 g/day), bicarbonate, Allopurinol, IV hydration, supportive care, electrolyte disturbances were corrected. After 20 days of treatment, leukocytes decreased at 20,000 /microL, renal function and serum electrolytes normalized. Therapeutic Committee of Hematology Clinic Cluj decided to start Imatinib, 400 mg/day. The treatment was well tolerated, after 3 months of treatment BCR-ABL/ABL was 10.8% and after 6 months of treatment BCR-ABL/ABL was 1.98%, both values being interpreted as "warning", according to 2013 European Leukemia Net Criteria. A test of kinase domain mutation was needed at that moment, but we couldn't perform it. After 6 months of Imatinib treatment, we decided to change the treatment to second generation tyrosine kinase inhibitors, Nilotinib. Two months later the patients started Nilotinib 2x300 mg/day. After a month of Nilotinib treatment, we performed a check-up (hematology, biochemistry, electrolytes, ECG). All the blood tests were in normal ranges. On ECG we observed that the patient developed QT prolongation syndrome, QTcB=483 msec, QTcF=445 msec. The change from baseline QTcF interval was about 50 msec. First, we checked the serum electrolytes which were in normal ranges, we asked the patient about concomitant medication or diseases and we found out that he didn't took any medication or medical condition with QT prolongation potential. In this case, we concluded that Nilotinib produced QT prolongation and we decided to decrease Nilotinib dose at 450 mg/day. We took a blood sample in order to perform a molecular test for BCR-

ABL/ABL. After a week, we received the BCR-ABL/ABL result: 0,159%. QT interval decreased, too, but not to normal ranges, QTcB=469 msec, QTcF=456 msec. We decided to decrease Nilotinib doses to 2x150 mg/day. After another week, both QTc intervals were in normal ranges, <450 msec and maintained this value. After 6 months of Nilotinib low dose (2x150 mg), the patient obtained a deep molecular response, BCR-ABL/ABL= 0.00065% (MR 4) and QTc interval maintained in normal ranges. After 2 years and a month after CML diagnosis, respectively after 17 months after starting Nilotinib, the patients accused hematuria. Abdominal echography showed a tumor mass into the urine bladder which was removed via cystoscopy. The anatomopathology examination diagnosed a neuroendocrine carcinoma of urinary bladder and the patient was referred to an oncologist who recommended chemotherapy, a Carboplatine-Etoposide regimen. After a collaborative discussion with the oncologist, we decided to interrupt Nilotinib during the aplasia inducing chemotherapy. Before stopping Nilotinib, we performed a molecular exam, and the patient maintained a MR4. After the second Carboplatine-Etoposide regimen, the patient died because a septic complication that appeared during aplasia.

Discussion

There are some ideas that we want to highlight related to this case report. Some of the issues are rhetorical questions.

First of all, the patient had a Chronic myeloid leukemia- chronic phase, high risk Sokal, high risk Hasford, low risk EUTOS treated with Imatinib (standard dose) for 8 months and the patients developed a "warning" response. Maybe he could have a better response from the beginning of the TKI treatment if he had been treated with Nilotinib from the first time. The Committee decided to treat the patient with first generation of tyrosine kinase inhibitors because of the age (73 years old) and because of financial restriction in our health system. Considering high risk Sokal and high risk Hasford categories at diagnosis, 2nd generation TKI could be administered.

After 8 months of treatment we couldn't perform the kinase domain mutation, maybe the patient had a partially resistant mutation to Imatinib. Some authors could have recommended an Imatinib dose escalation instead of changing to second generation TKI (8), other authors recomand a sooner change of the TKI to second generation if Nilotinib produced a "warning" or a "failure" response (9). We decided to change second generation TKI, Nilotinib. The patient had hypercholesterolemia which was controlled with Atorvastatin (the only statin permitted to be associated with Nilotinib because is not metabolized via cytochrome P450 CYP3A4 pathway). We dosed cholesterol and its fractions once at three months. Cholesterol level was not influenced by Nilotinib, despite its potential side effect on lipidic metabolism. In a Phase III study in newly diagnosed CML patients, 1.1% of the patients treated with 400 mg Nilotinib twice daily showed a Grade 3-4 elevation in total cholesterol. Lower grade elevation was observed in the group of patients treated with Nilotinib 300 mg twice daily, like our patient was treated. (4, 5)

After a week of treatment, the patient came for a complete blood count, we have done an ECG, QT interval prolongation was a random discover. When this patient developed this complication, we searched the literature, but we didn't find any clear protocols in case of QT prolongation. We checked for other causes of QT prolongation (other diseases, new introduced drugs, serum electrolytes modification) and in absence of these causes we conclude that Nilotinib produced QT prolongation. We decreased the dose until QT interval entered into normal ranges. It is remarkable that low dosed of Nilotinib produced such a good response (MR4) after 6 months of treatment, administered to a patient with "warning" response to a first generation TKI. This advocates for individualizing the dose for every patient, related to comorbidities, side effects and tolerability (10). The deep molecular response lasted for 17 months when, unfortunately, the patient developed a second cancer, neuroendocrine carcinoma of urine bladder. We consider that there is no relation between Nilotinib treatment and the second malignancy.

Conclusions

Nilotinib proved to be efficient in low doses (2x150 mg/day) and produced a deep molecular response (MR4). QT prolongation, as a Nilotinib

side effect was manageable by decreasing the doses.

CML treatment represents a continuous challenge, despite all the studies that have been done and published about the modern management of this disease. The comorbidities of the patients and potential side effects of the complex treatment of the disease determine us to consider that these patients should be approached by a multi-disciplinary team.

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Bone marrow hypoplasia secondary to tyrosine kinase inhibitors in chronic phase of Chronic Myeloid Leukemia – case report and literature review

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Abstract
According to 2016 WHO classification, Chronic Myeloid Leukemia (CML) is one of most studied entities in the last decades due to progresses in early diagnosis, monitoring and treatment options which lead to improved overall survival and progression free survival. We present the case of a young patient who initially had major molecular response (MMR) to Imatinib and lost it and received second generation TKI during which she develops bone marrow hypoplasia. The management of secondary hypoplasia is a difficult one. There are only 3 case reports published in which patient`s evolution was marked by severe complications which led to death.
Keywords: CML- chronic myeloid leukemia, TKI-tyrosine- kinase inhibitor, MMR= major molecular response, alloHSCT= allogeneic stem cell transplantation
Abbreviations:
CML= Chronic Myeloid Leukemia, TKI= tyrosine-kinase inhibitor, alloHSCT= allogeneic stem cell transplantation, MMR= major molecular response

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Introduction

Chronic myeloid leukemia (CML) is one of most studied MPNs in the last decades. The evolution of cytogenetic and molecular techniques have led to better understanding of role played by (9; 22) translocation and BCR-ABL1 transcript and to development of different target treatments. Imatinib, the first generation tyrosine-kinase and second generation TKIs (Dasatinib, Nilotinib, Bosutinib, and Ponatinib) led to an improved outcome for patients with chronic phase (CP) of CML, improved 5 year overall survival rate (ORR) and lower rate of progression to advanced phase. [1,2] Seldom, short and long term TKI treatment is complicated by grade 3-4 hematological and non-hematological adverse events. The following article will present the case of a young patient who received first and second generation TKIs, developed severe bone marrow hypoplasia with short lived response to Cyclosporine and needed allogeneic bone marrow transplant to control CML and hypoplasia.

Case report

We present the case of a 48 year old female patient known with Basedow-Graves disease since 1998 and diagnosed with CML-CP in January 2012 in a local hematology center. The diagnosis was confirmed by molecular test which showed b3a2 transcript with level of 100%. The patient was low risk according Sokal, Hasford and EUTOS scores and started on Imatinib 400 mg daily. At 3 months after CML diagnosis, patient was diagnosed with pulmonary tuberculosis and antituberculostatics were started. Major molecular response (MMR) was obtained at 6 months and maintained at 9 months. The loss of MMR was confirmed at 12, 15 and 18 months. Mutation analysis was negative.

According to 2013 European Leukemia Network (ELN) recommendations, the patient was considered treatment failure and switched to Dasatinib 100 mg daily and achieved MMR after 12 months. During Dasatinib treatment, patient presented recurrent severe neutropenia and thrombocytopenia which led to temporary discontinuation followed by restarting with reduced dose of 70 mg daily and 50 mg daily. After 15 months of Dasatinib, loss of MMR was confirmed. Mutation analysis was negative. We begin the search for unrelated HLA matched donor and patient started Nilotinib 600 mg daily. After 4 weeks of Nilotinib, patient had emergency admittance due severe metrorrhagia. Lab tests showed severe pancytopenia and Nilotinib was stopped. On admission in our department, clinic exam showed poor general state with severe pallor and extensive haemorrhagic lesions. The blood count confirmed pancytopenia. Coagulation, viral (HBV, HCV, HIV, EBV, CMV and B19 parvovirus) and tumoral screening (CA 15-3, CA 125, CEA) were negative. Bone marrow trephine showed hypocellular bone marrow (10-20%) due to fatty tissue replacement with rare areas of haematopoiesis. The molecular test showed MMR, cytogenetic exam showed normal karyotype and FISH exam was negative for additional cytogenetic abnormalities. The setting was suggestive for bone marrow hypoplasia secondary to TKI treatment.

At that time, there were only three published cases who have received corticosteroids, Cyclosporine and intravenous immunoglobulins (IVIG) with no response and infectious complications which lead to death. Our patient received corticosteroids and Cyclosporine, with improvement of blood parameters and transfusion independence after three months. The patient had molecular progression after 6 months of Nilotinib stop. Nilotinib was restarted but stopped after 2 months due to recurrent severe pancytopenia.

At next follow-up in our department, bone marrow biopsy was similar to the first one. Cyclosporine is restarted but with no response. Patient received an allo-HSCT after 12 months since the onset of bone marrow hypoplasia. At 12 months after allo-HSCT, the patient has normal blood parameters and sustained MMR.

Discussions

Acquired bone marrow hypoplasia may have different causes from viral infections to immunological disorders and certain drugs [4]. All previous mentioned causes were ruled out and the only hypothesis standing is hypoplasia secondary to TKI treatment. This is considered to be a very rare adverse effect [5] but in most cases leads to temporary stop of TKI.

As far as therapeutic management of secondary bone marrow hypoplasia is concerned, blood transfusions, corticosteroids and immunosuppressive drugs such as Cyclosporine followed by allo-HSCT in fit patients are the most used treatment options. In TKI induced hypoplasia, stopping TKI treatment is necessary. Corticosteroids are not very effective, the pancytopenia reappearing early after restarting the TKI [7]. Our patient received unrelated allogenic stem cell transplant with sustained MMR at periodic molecular follow-up.

The main issue that needs to be taken into consideration in this case is that we have no significant data for when is safe stop TKI without risk of disease progression in CML patients without an optimal response and severe adverse events.

Conclusions

Even if its represent a huge success in CML treatment, we must always have in mind that first and second generation TKIs can lead to severe adverse events such as bone marrow hypoplasia which can be associated with infectious or haemorrhagic complications but also with effects on disease outcome and progression, not well described in literature due to sparse cases. The risk of developing TKI resistance is bigger in a patient that has gone through multiple lines of treatment and needs temporary TKI discontinuation due to severe adverse reactions.

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