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Case Presentation
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T-Cell Lymphoma-Confusing Diagnosis, Long-Term Treatment

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Abstract

T-cell lymphomas are a group of diverse lymphomas including Anaplastic Large Cell Lymphoma, Mycosis Fungoides, Angioimmunoblastic T-cell lymphoma, Subcutaneous panniculitis-like T-cell lymphoma, Peripheral T-cell lymphoma not otherwise specified (NOS); still associated with unfavourable prognosis. Especially the diagnose of PTCL NOS is considered to be the challenge for the clinicians, because of the fact is made of exclusion. In this article we present short summarize of pathophysiology, prognostic factors and the management of the patient diagnosed with T-cell lymphoma. We demonstrate the case of the patient finally diagnosed with T-cell lymphoma NOS, to show how important is implementation to make proper differentiation with other diseases causing similar symptoms using all available diagnostic techniques such as histopathology, cytogenetic and molecular tests.

Keywords: T-cell lymphoma; Mastocytosis; C-kit mutation; Myelofibrosis; Autoimmune thrombocytopenia; Hepatosplenomegaly

Introduction

T-cell lymphoma, very rare and uncommon subtype of non-Hodgkin lymphomas is still associated with very poor prognosis in comparison to B- cell subtype [1]. Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) is kind of relapse and aggressive lymphoma associated with unfavourable prognosis. Among all T-cell lymphomas PTCL-NOS is still considered to be the challenge for clinicians and pathomorfologists mainly because of the fact that diagnosis of PTCL - NOS is made of exclusion [2]. Sometimes it is very difficult to make the right diagnose at the early stage of advancement due to the fact that there are no established diagnostic criteria. The biopsy of the suspicious skin changes is highly recommended by the National Comprehensive Cancer Network,

though many patients require several biopsies do make the final diagnose; process of the diagnosing can take even several years [3].

Case Presentation

On 8th of August 2020 56- year old men with the history of asthma, rheumatoid arthritis was admitted to Department of Hematology for diagnosis the leukopenia and anaemia. The peripheral blood disturbances were revealed on July 2020 and since this time the patient was under haematological supervision. At the admission he complained about general weakness, night sweats, weight loss (5 kg in 6 months). In physical examination among significant disorders benign skin lesions and hepatosplenomegaly (the spleen palpable 4 cm below the costal margin and the liver at the iliac spine) were detected. The Complete Blood Count (CBC) revealed normocytic anaemia with haemoglobin level (Hgb- 6,8 g/l), slightly decreased level of leukocytes and correct number of platelets (WBC-3,35 G/l, Plt-214 G/l). The microscopic blood smear revealed mild neutropenia (neutrophils constituted about 19% of leukocytes) and mild eosinophilia (40% of leukocytes). Due to the high level of immunoglobulin E, eosinophilia with correspondence of suspicious skin changes we performed the test towards the presence of the mutation of PDGFRA (negative) and examination for parasites (not detected). We revealed also the presence of the antibodies against Toxocara canis- we started the treatment with mebendazol. We excluded all the viral infections.

To extend haematological diagnostic of the two-line pancytopenia we perform bone marrow puncture, cytogenetic test and trepanobiopsy. In the myelogram, the bone marrow was low-cellularity, number of blasts was 2,8 %, with no features of dysplasia. Interestingly, we didn't reveal the presence of megakariocytes in the bone marrow smear. In trepanobiopsy the bone marrow with features of sclerosis and focal fibrosis was described; the histopatological result suggested myeloproliferative disease with features of fibrosis. Cytogenetic test revealed normal male karyotype (46, XY), with no disorders.

Due to the fact, that preliminary trepanobiopsy did not provide us significant information, three weeks later the patient was admitted again to the Department of Hematology to extend the haematological diagnostic. The patient complained about general symptoms. In physical examination besides hepatosplenomegaly, the aggravation of the papular rash on the skin was detected; affecting about 10% of the body surface area. The CBC was very similar to the previous one with haemoglobin level 7,2 g/dl. In microscopic blood smear in percentage distribution we observed increased number of lymphocytes (WBC- 3,14 G/l, neut-32%, lymph-52%, eos-8%). After finishing the treatment of toxocarosis we observed significantly decrease in the level of antibodies against T. canis. Due to the coexistence of hepatosplenomegaly, the result of histopathology characteristic to myelofibrosis we also performed molecular test towards the presence of BCR-ABL, JAK2, CARL, MPL. Our attention drew also the increased level of lymphocytes- it was only the disorder observed in percentage distribution, but it wasn't observed during last hospitalization.

We also excluded the Gaucher disease. After blood transfusion the patient was sent home.

After 7 days we received the results of molecular tests: BCR-ABL, JAK2, CARL, MPL were not detected. One month later the patient was admitted urgently to the Department of Hematology with the symptoms of thrombocytopenic purpura. At the admission he complained about general weakness and continuing of the weight loss. In physical examination we detected hepatosplenomagaly

(comparable to before), significant acceleration of skin lesions on the calves, trunk, arms and head **(Figure 1-5).**

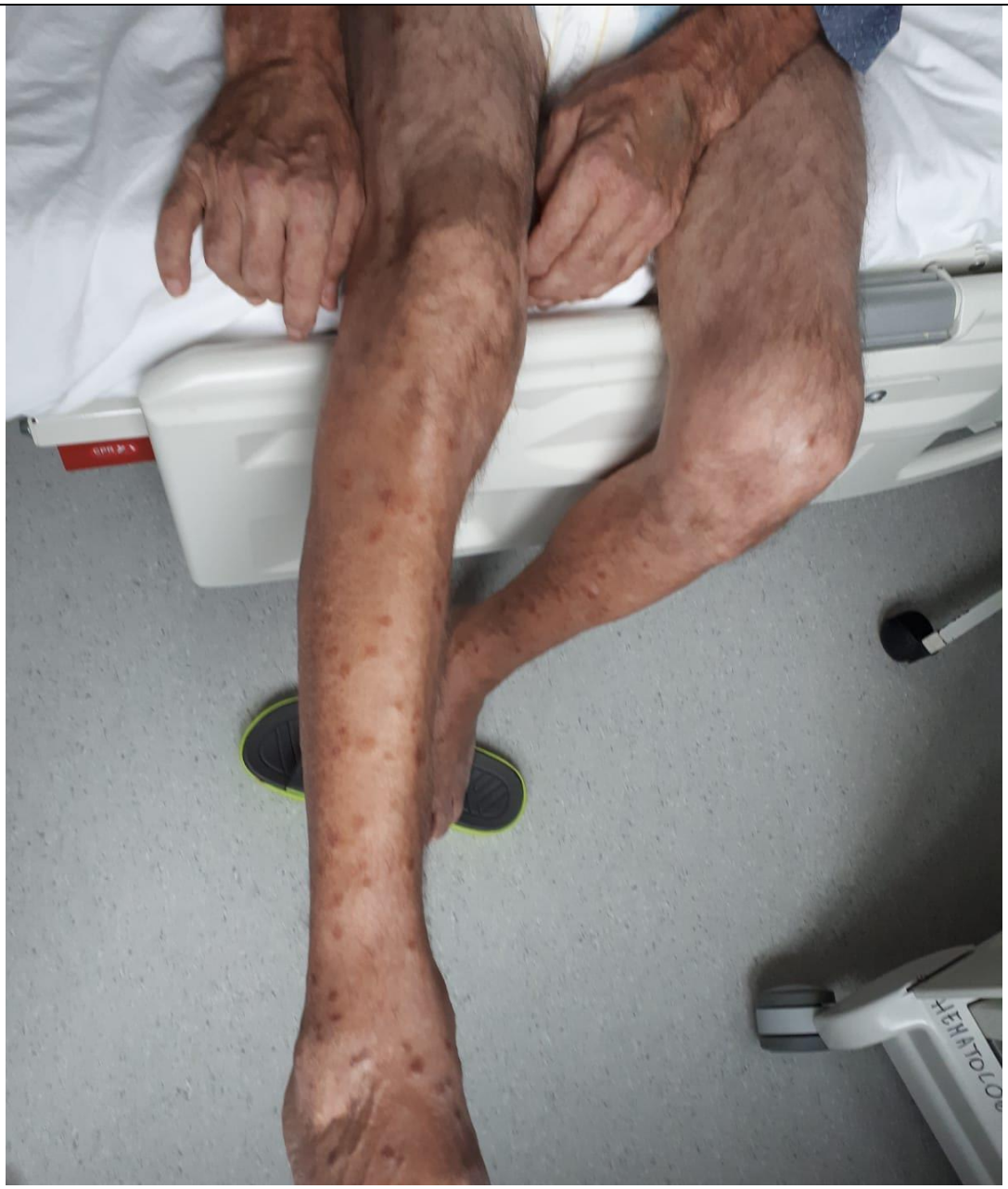

Figure 1

Figure 2

Figure 3

Figure 4

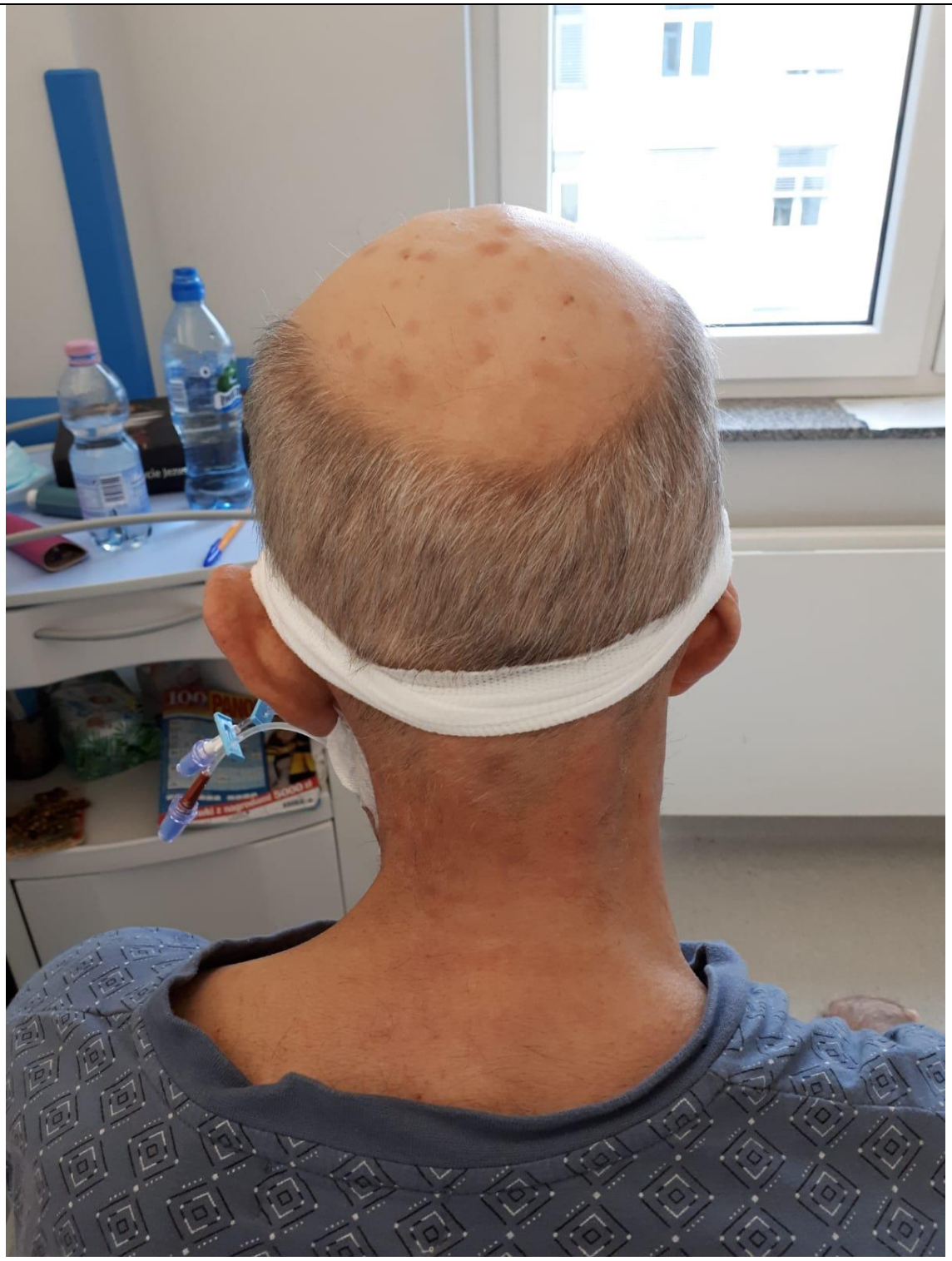

Figure 5: The acceleration of the skin lesions at the admission (all the photographs obtained with the patient's consent).

Interestingly, we observed significant changes in CBC in comparison to previous one(WBC-1,65 G/l, Hgb- 6 g/dl, Plt- 11 G/l). Biochemical tests revealed increased level of tryptase to 19 ng/ml. Due to the important clinical changes and progression of pancytopenia second time we performed bone marrow puncture and trepanobiopsy. In histopathology the features of sclerosis with

increased level of mastocytes up to 40% was described; according to pathomorphologist's opinion the whole picture suggests mastocytosis. To confirm this diagnose we performed the C-Kit mutation- the result was ambiguous, called by clinicians "in grey zone"; unfortunately it wasn't helpful to make the definitive diagnose. Finally we decided to perform the histopathology examination of the popular skin change. The result revealed the infiltration of small round cells with expression of CD2, partial expression of CD117, with negative expression of Mast Cell-Tryptase. According to the pathologist the whole picture was inconclusive, but can suggest cutaneous mastocytosis. Although the patient was preliminary diagnosed with mastocytosis, as clinicians we had objectives, especially because of the fact that all performed tests were still vague, so parallelly we decided to verify the diagnosis by another pathomorphologist.

During this hospitalization we observed significant intensification of skin lesion with itching and burning. The patient was given antihistamines drugs, hydoxyzin, prednizon to relieve the symptoms, with no clinical effect. Due to the suspicious of mastocytosis and fibrosis in trepanobiopsy we decided to started the treatment with pegylated interferon alpha (dosing 90 mcg two times a week started 09th Dec 2020 to 19th Jan 2021). After course with interferon we achieved significantly improvement of the skin lesions. However during the hospitalization the symptoms of thrombocytopenic purpura have worsened. We observed no significant increase in level of platelets after transfusion. We revealed the presence of anti-platelets antibodies; due to this fact the patient required transfusion of HLA- compatible blood products. Thrombocytopenia, stabilizing at the level of 3 to 5 G/l, was complicated by gastrointestinal bleeding, treated pharmacologically with proton pump inhibitor given intravenously. In treatment of thrombocytopenia we started methylprednisolone and immunoglobulin's (dosing 1 g/kg) achieving temporary increase in level of platelets up to 20 G/l. Another clinical problem we had to deal with was severe agranucocytosis complicated by pneumonia. We started the antibiotic therapy after receiving the results of microbilogical tests which revealed the growth of S. aureus and E. faecium, to targeted treatment- meropenem with wankomycin. Despite of staring wide- range antibiotic therapy we observed hypotension and features of septic shock. We gave fluids, pressor amines in constant intravenous infusion, oxygen therapy. After seven days of intensive treatment we achieved significant improvement of clinical condition which allowed us to withhold the noradrenalin infusion. Still we continued the target antibiotic therapy.

On 28th Jan 2021 we received the verification of the trepanobiopsy and histopathology of the skin changed examined by another pathomorfologist. The results were clearly unexpected and entailed significant clinical implifications. In trepanobiopsy the depletion of granulocytic line with majority of suppressor T lymphocytes was described. According to pathomorphologist's opinion this result wasn't characteristic to mastocytosis due to negative expression of CD25, moreover the expression of Mast-Cell-Tryptase (MCT) was present on several mastocytes- this above changes exclude the diagnose of mastocytosis. In histopathology of papular skin change the infiltration of lymphoid-like cells with negative expression of MCT, CD2(+), CD117(-) was revealed which finally excluded mastocytosis. However the majority of cells in the skin lesion were lymphocytes T helper CD4. The percentage distribution between lymphocytes TCD4 and T CD8 was 10:1. The proliferative index Ki67 was detected in 40% of cells. Conclusively the patient was diagnosed with unusual primary T-cell

lymphoma not otherwise specified (PTCL, NOS) with skin involvement and secondary massive bone marrow involvement and fibrosis. In treatment we started the preface with high doses of metylprednizolone, followed by two courses of chemotherapy based on fractionated cyclophosamide. After finishing this regimen of chemotherapy we didn't achieve the improvement in the number of platelets- it still fluctuated between 3 to 10 G/l. The patient was dependent to HLA- compatible blood products transfusion. Due to the fact that the patient suffered from agranulocytosis and thrombocytopenia which disqualified him from aggressive chemotherapy, no effect to steroids and immunoglobulin's we decided to order eltrombopag from "emergency access to drug technologies". The procedure finished successfully. We started the dosing with 25 m daily escalated to 75 mg. Despite of all conducted treatment we haven't achieved satisfactory results- the CBC still revealed two- line pancytopenia (WBC- 5,8 G/l, Hgb- 8,7g/dl, Plt- 6 G/l). The patient was consultated by the surgeon and qualificated to splenectomy. After transfusion of platelets and two courses of immunoglobulin's patient underwent splenectomy (10th Mar 2012). In the histopathological examination of the spleen the features of haematopoiesis with quite a large amount of lymphocytes T was confirmed; however the whole picture suggested rather the myeloproliferative neoplasm.

After the surgical procedure we observed the fluctuation in the level of platelets- on fourth day after splenectomy the number of thrombocytes increased rapidly to 40 G/l, then dropped to 8 G/l. The haemoglobin level stabilized between 9 and 10 g/dl; we observed mild leukocytosis (WBC- 16 G/l). We continued the treatment with eltrombopag (75 mg daily) with prednisone. We achieved the normalization of the level of thrombocytes (15 G/l), independence from transfusions, resolution of thrombocytic purpura. On 25th Mar in state of general improvement the patient was discharged home. On 25th May 2021 the patient was urgently admitted to Department of Hematology because of general weakness, oedema, ascites, persistent severe papular skin changes restricted to 50% of the body surface area; mainly situated on calves abdomen and arms. In physical examination we detected significant progression of hepatomegaly (15 cm below the costal margin), the features of ascites with positive flutter test. The CBC revealed leukocytosis (WBC- 79 G/l) with a predominance of neutropfils (37 G/l) and monocytes (22,3 G/l). Haemoglobin stabilized at the level of 11 g/dl, the number of thrombocytes was 20 G/l. Due to significant CBC disturbances we decided to perform bone marrow puncture, trepanobiopsy, cytogenetic and molecular test as well, as taking into account the essential suspicion of myeloproliferative neoplasm.

In the cytological evaluation of the myelogram the bone marrow was medium- cellularity with addition of peripheral blood; no megakariocyte was found. Blasts constituted 2,6% of all cells. In trepanobiopsy the bone marrow with significantly increased cellularity (about 90%) and features of sclerosis was described. The histopathology examination revealed also immature cells of granulocytic lineage, scattered lymphocytes and polymorphic megakariocytes. Cells with the expression of CD34+ include about 10% of all cells. The other laboratory tests performed during this hospitalization confirmed acute liver injury. They revealed significant increase in the level of alanine aminotransferase to 200 U/l, total bilirubin up to 4,54mg/dl with predominance of direct bilirubin, hemorrhagic diathesis resulted in elongation on prothrombin time to 42 sec., APTT up to 96 sec., decrease in fibrinogen to 50 mg/dl.

We excluded cholestasis, portal vein thrombosis, HBV, HCV, HIV and CMV infection which can cause such exacerbation. Due to positive EBV IgM antibodies we performed also molecular test which finally confirmed the EBV infection. The patient was consultated by the hepatologist- we conducted hepatoprotective drugs, ursodesoxychlic acid, albumin supplementation, diuretics, antispasmodics. In the next few days we observed increasing level of ammonia; the patient complaint about dyspnea. Due to mild effect after diuretic treatment we performed paracentesis. The patient required the transfusion of cryoprecipitate (dosing 1j/10 kg every 48 hours).

Due to increasing leukocytosis, significant suspicion of coexistence of myeloproliferative neoplasm we performed again the bone marrow puncture with flow cytometry. The examination revealed increased number of monocytes (>94%) with CD64+, CD14+^{bright,} CD16- phenotype; the whole result suggested the Chronic Myelomonotic Leukemia (CMML). Unfortunately despite of all conducted treatment we observed increasing number of leukocytes, worsening liver parameters, aggravation of haemorrhagic diathesis complicated by bleeding from suprascapular artery with the formation of hematoma and follow-up anaemia (Hgb- 6,9 g/dl). We observed critically prolonged APTT to 97, INR to 4,5; decrease in fibrinogen to 41 mg/dl. Considering high operational risk the patient was qualificated for selective embolization of suprascapular artery supported by intravenous hydration, blood and crioprecypitate transfusion. The surgeon evacuated 200 ml of blood, mainly clotted. In next few hours we observed the accretion of hematoma. Next day patient complained about dyspnea; we observed decrease in saturation to 80% requiring oxygen therapy; finally after over month of hospitalization the patient died.

Discussion

In described case very interesting was inconclusive correspondence between the trepanobiopsy and the result of the histopathology of the skin change. Trepanobiopsy performed on Dec 2020 revealed the features of sclerosis and focal fibrosis. Although mielofibrosis is mainly characteristic to myeloproliferative disease it can also coexisted with T-cell lymphomas. Sujatha. A. et al. [4] described a case of a patient diagnose with T-cell lymphoma with mielofibrosis in histopathology, which interestingly subsided completely after achieving complete response to targeted anti-lymphoma therapy [4]. The pathogenesis of mielofibrosis in T-cell lymphoma is still unexplained, but the researchers have confirmed that major role in this process plays transforming growth factor-beta1 (TGF-beta1) [5]. The coexistence of T-cell lymphoma and mielofibrosis, still very rare, should be always carefully evaluated for lymphoma.

The major problem was the differentiation between mastocytosis and T- cell lymphoma.

Yee Soo Choe et al. [6] conducted a study including 52 patients with Peripheral T-cell lymphoma investigating the expression of C-Kit mutation in these patients using PCR-single-stranded conformational polymorphism followed by direct DNA sequencing. Weak expression of C- Kit mutation was detected in 30.8% of patients. The mutation in exon 11 or 13 was only found in 5,8% of cases. Conclusively due to weak expression in T-cell lymphoma the C- kit mutation does not seem to be a new therapeutic approach in treatment [6]. When the patient was definitively diagnosed with PTCL, great challenge for clinicians was the choice of the proper treatment. We had to take into consideration other parallel clinical problems especially the coexistence of autoimmune thrombocytopenia (anty-HLA). This could

significantly increase the number of haemorrhagic complication therefore we could not start the treatment with first line recommended regiment of chemotherapy, CHOP-E (cyclophosphamide, hydroxyduonorubicin, oncovin, prednisone, etoposide) [1]. To minimalize the risk of such complications we conduct preface with high doses of metylprednizolone, followed by two schedules of COP chemotherapy. Additionally we started also the eltrombopag.

The next clinical problem in this case was acute liver injury. After excluding the progression of main disease, hepatitis viral infection we suspected that acute liver injury was caused by EBV infection. Our hypothesis was supported by the fact that increasing the liver parameters was parallel with increase in the number of EBV DNA. Due to the fact, there are no casual treatment of EBV infection, we started the hepatoprotective drugs observing gradual improvement of liver parameters. Another clinical problem we had to deal with was increasing leukocytosis with predominance of monocytes. We took into consideration the influence of EBV infection and overlapping the myeloproliferative disease. To exclude the myeloproliferative neoplasm we performed molecular test toward the presence the JAK2, CARL and MPL mutations, which was negative. The trepanobiopsy revealed the bone marrow with significantly increased cellularity (about 90%) and features of sclerosis. The flow cytometry of the bone marrow suggested the Chronic Myelomonotic Leukemia.

Finally the patient died diagnosed with two cancer diseases, complicated by acute liver injury and severe haematoma diathesis. In such complicated case of the patient many questions still remain unanswered.

Conclusion

T-cell lymphomas are still very rare but associated with unfavourable prognosis. To supervise the patients with suspicious skin changes, diagnose and conduct the proper treatment we need the cooperation of dermatologist, pathologist and haematologist to finally improve the life expectancy of these patients.

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