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Case Report

A Liver Transplanted Patient with Severe Pancytopenia -Reversed by Change of Immunosuppressive Regimen

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Abstract

Patients with colorectal cancer with unresectable liver metastases have an expected median overall survival of approximately 30 months with current standard treatment with palliative chemotherapy. Liver transplantation for these patients has showed encouraging results and has gained increased interest in recent years, currently being investigated in several clinical trials. We report a male patient who received liver transplantation due to non-resectable colorectal liver metastases. Shortly after the introduction of sirolimus the patient presented with severe pancytopenia with myelodysplastic syndrome-like bone marrow features, and was given a dismal prognosis. The condition was reversed when the immunosuppressive regimen was changed to cyclosporine. We cannot exclude the possibility of myelodysplastic syndrome in this case, but bone marrow failure with dysplastic features induced by immunosuppressant drugs in a patient who was previously treated by chemotherapy is a likely alternative explanation. This case illustrates the clinical relevance of sirolimus/tacrolimus induced pancytopenia, especially in patients treated with chemotherapy prior to transplantation. The bone marrow failure may be reversible with a change in the immunosuppressive regimen, as shown in this case.

Abbreviations: CRC: Colorectal Cancer; OS; Overall Survival; LT: Liver Transplantation; PR: Partial Response; PD: Progressive Disease; WBC: White Blood Cell Count; ANC: Absolute Neutrophil Count; TRC: Thrombocytes; Hb: Hemoglobin; MDS: Myelodysplastic Syndrome; CHIP: Clonal Hematopoiesis Of Indeterminate Potential

Introduction

Patients with Colorectal Cancer (CRC) with unresectable liver metastases have an expected median Overall Survival (OS) of approximately 30 months with current standard treatment with palliative chemotherapy [1,2]. Liver Transplantation (LT) for these patients has gained increased interest in recent years and is currently being investigated as a treatment option in several trials (SECA II NCT01479608, RAPID NCT02215889, TRANSMET NCT02597348, SECA III NCT03494946, Toronto Protocol NCT02864485, LIVERT(W) OHEAL NCT03488953, COLT NCT03803436, SOULMATE NCT04161092). Published results show an estimated 5 year OS of 60-80 % in selected patients [3-5].

Case Report

A 53 year-old male with no history of hematological disease was by September 2016 diagnosed with left-sided colon cancer. He underwent laparoscopic rectosigmoidal resection. CT scan at time of diagnosis revealed a total of 20 liver metastases, involving all segments except segment 1; the largest lesion measured 49 x 65 mm. There were no signs of extra-hepatic metastases. Due to the hepatic tumor load, liver resection was not a treatment option, and palliative chemotherapy was commenced. The blood panel was within normal limits before initiation of chemotherapy (Figure 1). He received Nordic FLIRI (irinotecan + bolus 5-FU) [6] + bevacizumab with initial partial response (PR). Due to neutropenia treatment intervals were increased from two to three weeks form the 7th cycle, and pegfilgrastim was administered from cycle 8. After eight months of treatment he had a chemotherapy holiday, and 11 weeks later he started second line treatment with Nordic FLOX (oxaliplatin + bolus 5-FU) [7] due to progressive disease (PD). Response evaluation after four cycles showed PD, and third line treatment with Nordic FLIRI+ panitumumab was initiated. FDG-PET/CT did not reveal any extra-hepatic disease manifestation, and he was accepted for inclusion in the SECA Arm D LT study [8]. After two weeks on the transplant waiting list, June 13th 2018, he underwent allogeneic LT from a deceased donor. In the SECA Arm D study protocol extended criteria donors were used. In this case the donor graft was hepatitis core and surface positive, thus life-long entecavir treatment of recipient was indicated. The first post-operative day ultrasound revealed hepatic artery thrombosis, and he was re-operated with embolectomy and re-anastomosis of the artery and the bile duct. The remaining post-operative period was uneventful.

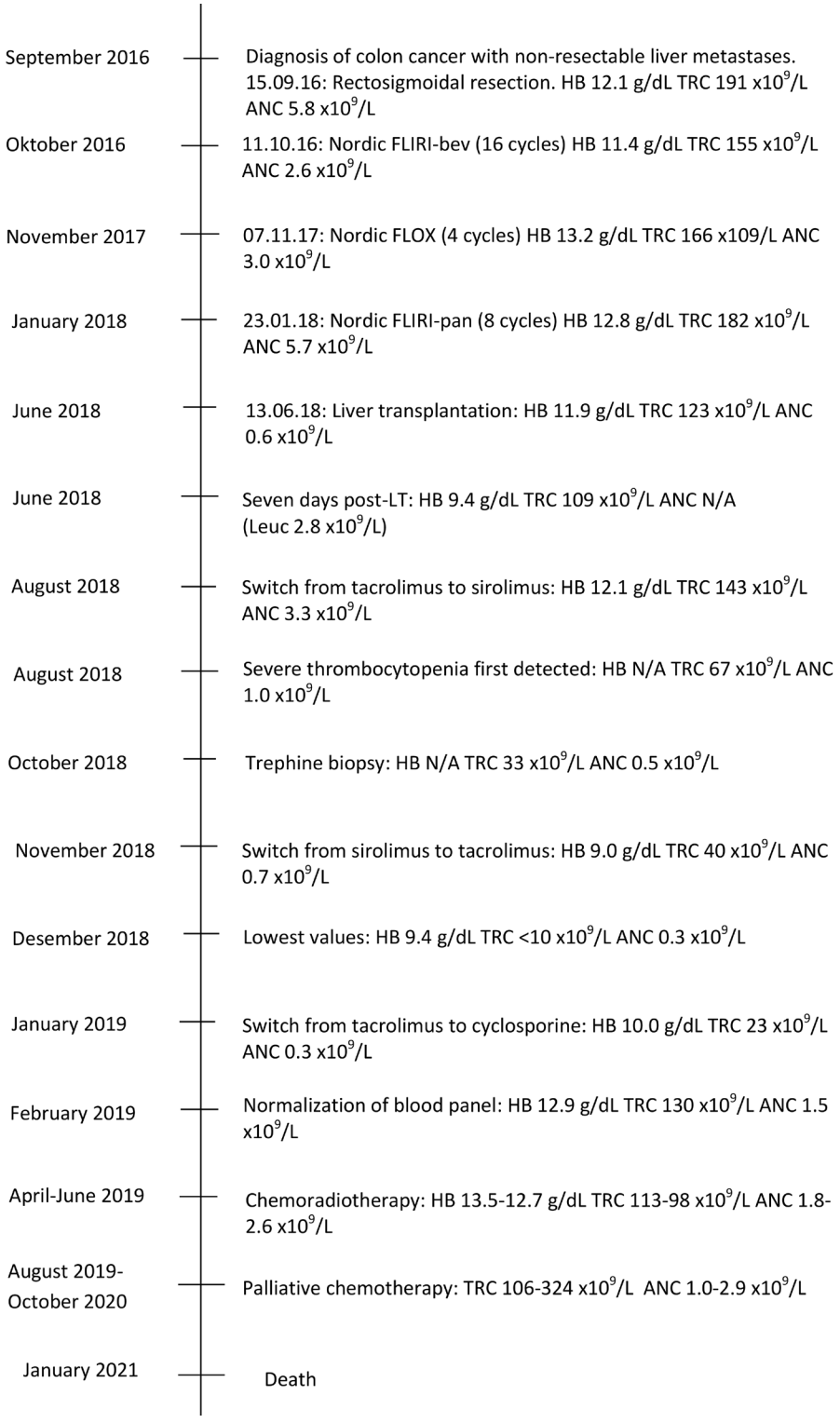

Figure 1: Timeline showing key treatment and examination points with corresponding hematological values at time of diagnosis of colorectal cancer until death.

The immunosuppression protocol in this study consisted of induction with basiliximab, corticosteroids, mycophenolate, and tacrolimus the first 4-6 weeks, then conversion from tacrolimus to the Mammalian Target of Rapamycin (mTOR) inhibitor sirolimus, aiming for a trough level of 5-10 µg/ml in the first 4 weeks and 10-12 µg/ml thereafter. Corticosteroids were tapered to zero within six months after LT. In the presented case the switch from tacrolimus to sirolimus was done August 15th 2018, i.e. nine weeks after LT. The hematological panel was at that time completely normal (Figure 1). Two weeks later, August 30th, the blood panel showed cytopenia with white blood cell count (WBC) 1,7 x 10^9/L, absolute neutrophil count (ANC) 1,0 x 10^9/L and Thrombocytes (TRC) 67 x 10^9/L (Figures 2A-B). Two weeks later the blood panel showed hemoglobin (Hb) 11,9 g/dL, WBC 1,6 x 10^9/L, ANC 0,7 x 10^9/L and TRC 60 x 10^9/L. Medication-induced cytopenia was suspected, and mycophenolate mofetil as well as trimethoprim/sulfamethoxazole was discontinued. The sirolimus concentration at this time was 6,2 µg/L. October 10th the blood panel showed Hb 9,3, TRC 10 x 10^9/L, WBC 2,6 x 10^9/L and ANC 0,7 x 10^9/L. A hematological evaluation was scheduled (Table 1).

Modality	Evaluation
Blood smear	Erythrocytes showed anisocytosis with macrocytosis and occasional dacrocytes. Thrombocytes also showed anisocytosis and variable granulation with a population of thrombocytes being clearly hypogranular. Granulocytes were nonconspicuous, and there were only a few large granular lymphocytes.
Bone marrow smear	The cellularity was above average. Megakaryocytes were normal in number, but more than 10% showed dysplastic features like micromegakaryocytes with non-lobulated nuclei and megakaryocytes with widely separated nuclei. The erythropoiesis was slightly increased and accounted for 35% of the cellularity. The erythropoiesis showed megaloblastoid features with a relative lack of pyknotic erythroblasts, and more than 10% of the erythroblasts were dysplastic with nuclear irregularities and budding. Ring sideroblasts were not present. The granulopoiesis was differentiated with no dysplastic features, but was remarkable by a relative low number of segmented granulocytes. No sign of metastasis was disclosed.
Trephine biopsy	Cellularity was 50-60% which was considered slightly hypercellular. Dysplastic features as described in the bone marrow smear were confirmed.
Conclusion	The assessment disclosed ineffective hematopoiesis with dysplastic changes in the erythropoiesis and thrombopoiesis indicating myelodysplasia. Cytogenetic assessment was considered mandatory.
Genetics	Karyotyping of a bone marrow aspirate showed a normal male karyotype; 46, XY. In October 2020 targeted next generation sequencing (TruSight Myeloid Sequencing Panel, Illumina) of the bone marrow aspirate showed a DNMT3A mutation (c.2645G>A p.Arg882His) with a variant allele frequency (VAF) of 7,5%.

Table 1: Hematological examinations.

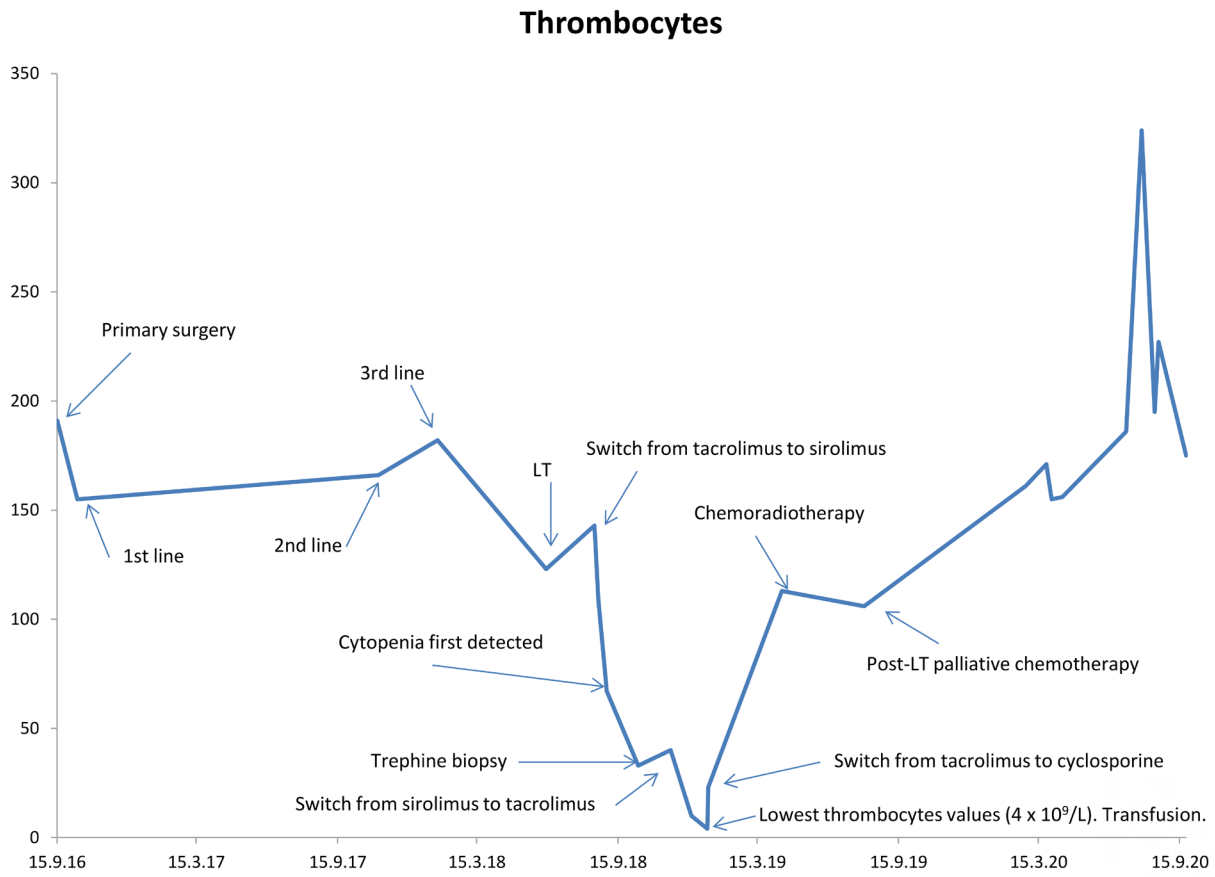

Figure 2A: Curve depicting thrombocytes values in relation to key treatment and examinations points.

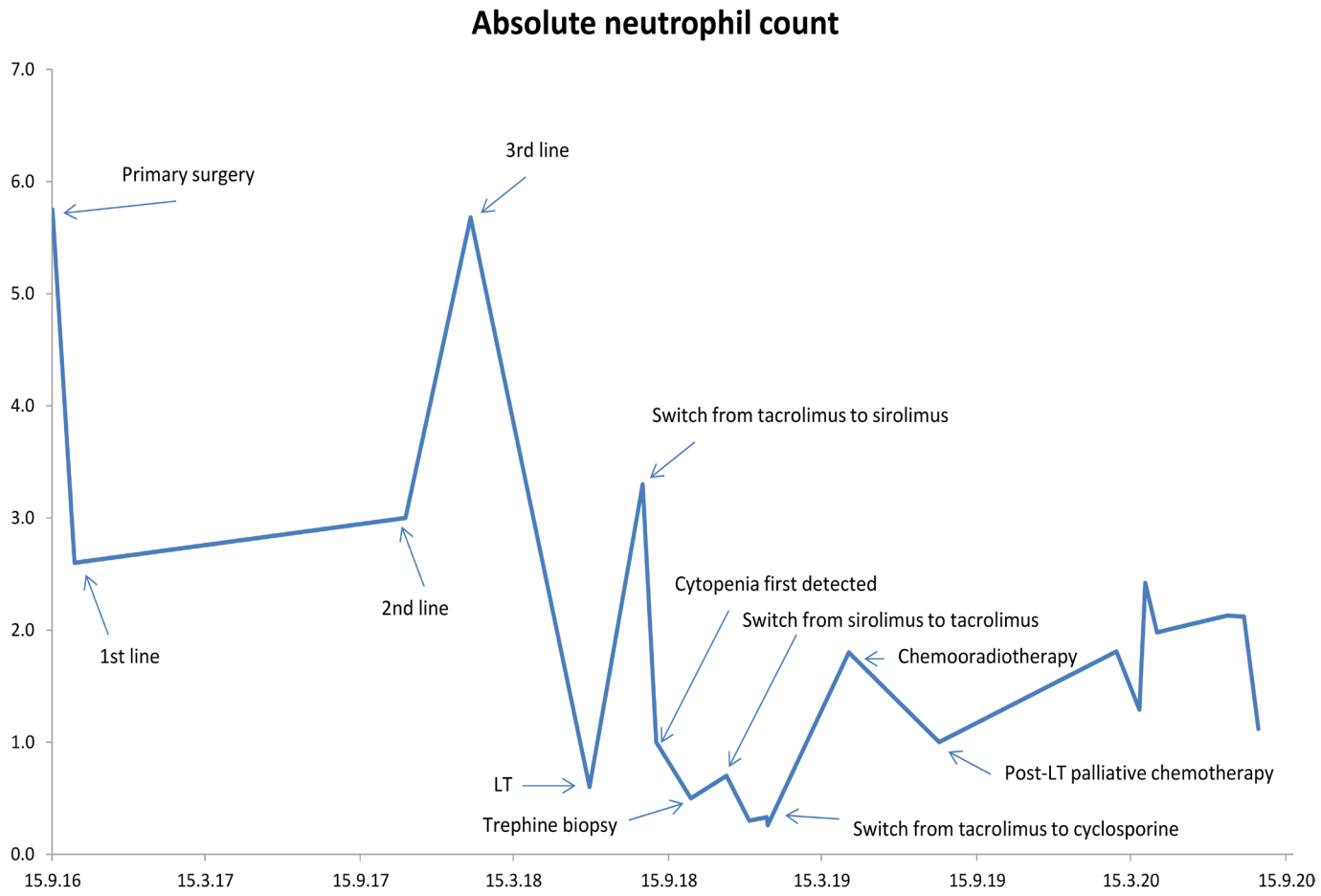

Figure 2B: Curve depicting absolute neutrophil count in relation to key treatment and examinations points.

Due to prolonged cytopenia a switch from sirolimus to tacrolimus was done November 22nd 2018 without any improvement of the condition. Immunosuppression was by January 10th 2019 changed from tacrolimus to cyclosporine aiming at a plasma concentration of 100-150 ng/ml. Prednisolone 20 mg daily was added. By February 13th the blood counts were Hb 12,9 g/dL, TRC 106 x 10^9/L, WBC 6,1 x 10^9/L, and ANC 2,6 x 10^9/L, and within the following few weeks the TRC and ANC counts were close to normal (Figures 2A-B). The spring of 2019 the patient was diagnosed by pelvic MRI with an advanced pelvic recurrence, and was treated with chemoradiotherapy, 2 Gy x 25 in combination with bolus 5-FU with the intent of curative surgery. Response evaluation with CT and pelvic MRI scans showed minimal response to the treatment, and peritoneal metastases had appeared. Curative treatment was thus not an option, and palliative chemotherapy with irinotecan + panitumumab was commenced. He had PR on this regimen for around one year, due to neutropenia after the forth cycle he had a dose reduction and eventually with pegfilgrastim support. After progression on this regimen he was treated for a short period with NORDIC FLOX in combination with bevacizumab before he passed away in early January 2021, approximately 20 months after recurrence and 16 months after the start of palliative chemotherapy. The patient signed a written consent for publication of this case report prior to his passing.

Discussion

Sirolimus and other immunosuppressive agents may cause leukopenia and thrombocytopenia of various degrees [9,10], but our patient had severe (CTCAE grade 4) thrombocytopenia as well as neutropenia and anemia presenting shortly after the introduction of sirolimus. The bone marrow assessment revealed ineffective hematopoiesis with dysplastic features suggestive of Myelodysplastic Syndrome (MDS). Chemotherapy prior to LT could have been a plausible cause of MDS in this case. However, the time from start of chemotherapy to the development of bone marrow failure in this case is very short compared to what has been reported in chemotherapy-related myeloid malignancies [11]. Secondary myeloid malignancies due to alkylating agents typically appear after 5-7 years as MDS which may develop into acute myeloid leukemia. Myeloid malignancies developing 2 years after chemotherapy are typically acute myeloid leukemia and are related to topoisomerase agents. Furthermore, karyotyping disclosed a normal male karyotype. However, cytogenetic abnormalities is not a prerequisite for a MDS diagnosis as clonal cytogenetic abnormalities are observed in approximately 50% of MDS cases [12]. In search of support for a MDS diagnosis in this case we performed next generation sequencing of a bone marrow aspirate from October 2018 and found a DNMT3A mutation with a VAF of 7,5% as the only abnormality. We do not consider this finding as a definitive proof of myeloid malignancy as DNMT3A mutations is one of the most common abnormalities in clonal hematopoiesis of indeterminate potential (CHIP) [13]. We cannot exclude the possibility of MDS in this case, but bone marrow failure with dysplastic features induced by immunosuppressant drugs is a likely alternative explanation. This notion is supported by the prompt improvement of blood counts after change of the immunosuppressive regimen. This case illustrates the importance of considering modification of the standard sirolimus/tacrolimus based regimen to cyclosporine, in patients developing bone marrow failure with MDS-like features. Without the change in immunosuppression regimen he had not been given the option of preoperative curative intended chemoradiotherapy, and later palliative chemotherapy. He had most likely had a short life expectancy, but instead survived for 26 months after the bone marrow failure and died due to relapse of metastatic CRC. This case-report illustrates the clinical relevance of sirolimus/tacrolimus induced pancytopenia, especially in patients treated with chemotherapy prior to transplantation. The bone marrow failure may be reversible as shown in this case; change in the immunosuppressive regimen may improve the situation dramatically and provide extended survival.

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