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Long-Term Survival in the Concomitant Evolution of Two Cancers: The Idiopathic Myelofibrosis and the Clear Cell Renal Carcinoma; A Case Report

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Abstract

Introduction: The association of chronic myeloproliferative neoplasia with urogenital cancer is rare (1.6% - 1.9%), with the death risk of 1.21 - 2.28 times higher in patients with solid cancer and chronic myeloproliferative disease.
Case Presentation: We present the case of a patient diagnosed with triple-negative idiopathic myelofibrosis treated and monitored at the Department of Hematology of the Clinical Emergency County Hospital, Brasov, Romania. After five years of idiopathic myelofibrosis, which was treated with hydroxyurea, a second solid neoplasia was identified as left renal cell carcinoma in Robson stage I. The complete remission of the renal carcinoma was achieved with the left nephrectomy sustained for a duration of approximately four years, overlapping with the partial remission of myelofibrosis under treatment with ruxolitinib. The recovery of the renal carcinoma significantly influenced myelofibrosis therapy and subsequently led to the patient's development. The global survival, in this case, is 124 months for myelofibrosis and 64 months for the concomitant evolution of the two cancers.
Conclusions: Despite a number of peculiarities (age at diagnosis and complications during the treatment of two cancers), the patient had a prolonged survival.

Keywords: Carcinoma, Hydroxyurea, Myelofibrosis, Nephrectomy, Remission, Renal Cell, Ruxolitinib, Primary, Survival

1. Introduction

Idiopathic myelofibrosis, an entity of chronic negative myeloproliferative malignancies Ph-negative/bcr-abl negative (1), is a clonal proliferation of the pluripotent hematopoietic stem cell (2), characterized by an abnormal cytokine expression. In 90% of the cases, it is associated with three mutations of JAK2, CALR, or MPL, medullar fibrosis, and inefficient extra-medullar hepatosplenic hematopoiesis, as well as splenomegaly in 89% of the cases (3), constitutional phenomena in 27% of the cases (3), and anemia (Hb below 10 g/dl) in 35% of the cases (3) along with leucoerythroblastic appearance.

Idiopathic myelofibrosis is estimated to have an annual incidence of $0.1 - 1 \times 10^5$ cases in Europe, with an average diagnosis age of 69 - 76 years (4). The mean survival time in idiopathic myelofibrosis is six years although it is dependent on the risk group according to the dipss5 score from 14.2 years for those with a low risk to only about 1.5 years for those with a high risk (5). The survival time reduces in idiopathic myelofibrosis under the conditions of thrombo-hemorrhagic events or progression to acute leukemia (Table 1) (6).

Table 1. Survival Time in Idiopathic Myelofibrosis and Renal Cell Carcinoma

Variables	Literature Data	The Present Case Report
Age, y	69 - 76	59
Overall Survival for idiopathic myelofibrosis, mo	72	124
Overall survival for renal cell carcinoma, mo	60	64

With the exception of allogeneic hematopoietic stem cell transplantation, current therapies do not induce long-term free remission (7). Ruxolitinib, a Janus kinase (JAK1/JAK2) inhibitor, demonstrated superiority to the best available therapies in terms of disease control and survival, with a 33% reduction in the death risk according to

COMFORT-II (8).

Clear cell renal carcinoma (Grawitz tumor) accounts for 60% of all renal cancers and 3% of the total adult cancers, with a 66% survival at five years if diagnosed with Robson stage I (9). Nephrectomy is the therapeutic attitude in stage I while in advanced stages, chemotherapy and/or biological therapies are the therapeutic options that can reduce response rates and metastatic evolution.

Sunitinib is an RTK tyrosine kinase inhibitor in metastatic renal cell carcinoma, inducing a global survival rate of 30.4 months in clinical studies.

The data about the concomitant evolution of myeloproliferative neoplasm and solid cancer are limited so far. The data in this field were presented by a Danish group in 2012 based on a retrospective analysis of real-life patients diagnosed with myeloproliferative neoplasms during 1977 - 2008.

2. Case Presentation

We present the case of a 59-year-old patient who presented at the Hematology Ambulatory of the Brasov County Emergency Clinical Hospital in December 2007.

The non-smoker patient without significant antecedents, with no history of family aggregation of genetic diseases or cancer, presented the following signs for three months before her hematologic examination: fatigability, equilibrium disorders, night sweats, weight loss of about 5%, abdominal discomfort, and feeling of gastric fullness. The patient was clinically ECOG-1, IK-90%, without any peripheral adenopathies, no hepatomegaly, and spleen at 2 cm under the ribs.

The hemoleucogram, biochemical, and ultrasound (US) examination results are shown in Table 2.

Ultrasound and CT scan were performed at the hospital. The devices had certificates in accordance with the requirements of the ISO 9001 Quality Management System.

The medullary aspiration was clear. The histopathological examination of the osteomedullary biopsy (Figures 1 and 2) described a hypercellular marrow with granulocytic and megakaryocyte serial hyperplasia and reticulinical myelofibrosis in focal confluence. Myelofibrosis was grade 1 of 3 (10).

The molecular examination in December 2007 consisted of determining the JAK2 and BCR/ABL mutations, both of which were negative. Molecular biology tests were performed by Ritus Biotec Laboratory, Brasov, Romania. This center has been the member of European Leukemia Network since 2015. It is registered by the United Kingdom National External Quality Assessment Services for Leukocyte Immunophenotyping and is an accredited center by the European LeukemiaNet.

Table 2. Hemoleucogram, Biochemical, and Ultrasound Examination Results

Variables	Values
Age, y	59
Sex	Female
Blood cells	
Hb, g/dL	11.2
WBC, /L	7800
PLT, /L	716000
Biochemical parameters	
LDH, U/L	801 (normal limit 225)
Feritine, cmg/L	239.4
Epo seric	normal
Abdominal US	
Spleen diameter, cm	14.9

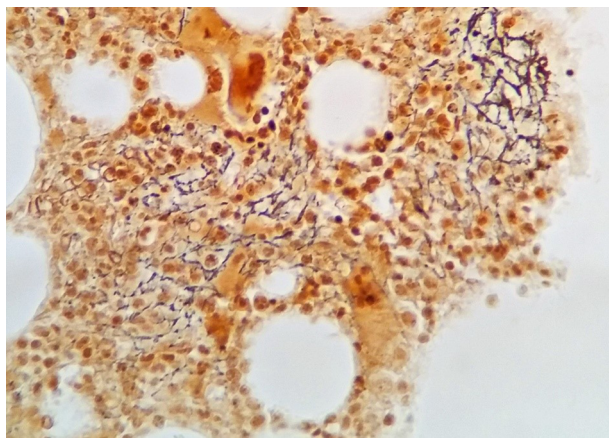

Figure 1. BMO-Color blades Gomory Ob.20x. Reticulum fiber with a tendency for confluence

By correlating the clinical, morphological, histopathological, and molecular biology data, the diagnosis of JAK2-negative idiopathic myelofibrosis was established. According to the Lille prognostic score, applicable to patients with idiopathic myelofibrosis since 2007 by including only two factors, the patient was in the low-risk class with a mean survival of 93 months. The subsequent recalculation of the prognostic score according to the IPSS international prognostic score (11) with five variables included the patient in the intermediate risk category 1 with a mean survival of 7.9 years.

Between December 2007 and December 2012, the patient underwent cytoreductive treatment with hydroxyurea, with the goal being to maintain the spleen size and platelet number within normal limits. During this period,

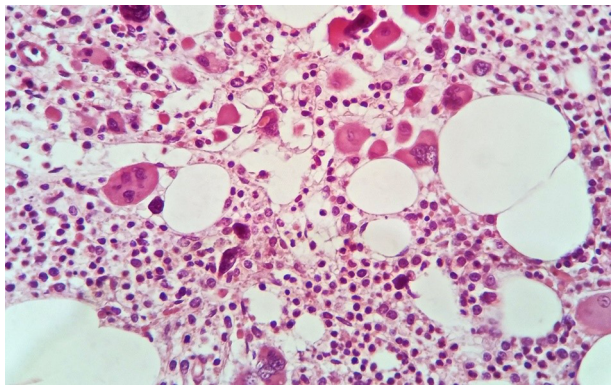

Figure 2. BMO-Color blades H.E.Ob.40x. Megakaryocytes with compacted layout, pleomorphic appearance, and hyperlobular nucleus

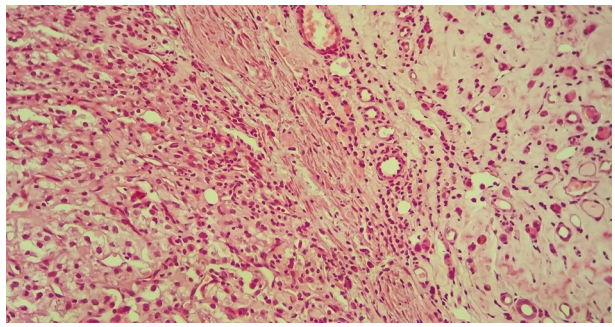

Figure 3. H.E. Ob.20x. In the center is the fibrous pseudo-capsule with reactive inflammation, which made the separation between tumor (left) and non-tumor renal tissue (right)

the patient did not require substitution treatment and the hemoglobin level was constant over 10 g/dL.

In the fifth year of development of idiopathic myelofibrosis, the following signs were observed: the accentuation of constitutional symptoms (asthenia) and progressive splenomegaly, the apathy of myeloblasts 2% on the peripheral blood smear at serial determinations and at the BMO 2 degree myelofibrosis. In December 2012, the size of the spleen was measured in order to initiate treatment with JAK1/JAK2 inhibitors. Splenomegaly of 17/15/7 cm and a tissue mass developing in the inferior renal pole with a heterogeneous contrast ratio of 42/49/42 cm without extension to adjacent tissues were observed in the abdominal ultrasound.

In February 2013, a left nephrectomy was performed with block resection of the Gerota fascia, the left adrenal gland, and the lymph node according to the protocol in the case of suspected kidney cancer. The histopathological examination confirmed the diagnosis of kidney carcinoma with clear infiltrative cells in the capsule (Figure 3). Being in the T3pNxMx stage, it did not require chemotherapy or postoperative biological therapies.

In 2014, the patient had an increase in constitutional symptoms (asthenia, weight loss over 10%, night sweats), and anemia (Hb = 9.8 g/dL), thrombocytosis (730000/L) despite treatment with hydroxyurea, leukocytosis with a leucoerythroblastic picture and 2% myeloblasts. The TC examination showed splenomegaly of 19.2/13/8 cm, with no signs of tumor recurrence post left nephrectomy. The molecular examination was repeated, showing all three mutations (JAK2, CALR, MPL) were negative and the patient was in the category of the 10% triple-negative cases (12). The recalculation of the DIPSS prognostic score (5) included the patient in the intermediate category 2 with an average survival of 35 months.

Due to the progressive splenomegaly and constitutional symptoms, we decided to initiate therapy with Ruxolitinib 20 mgx2 /day. In patients with idiopathic myelofibrosis, it is the only therapy evaluated in the context of a randomized clinical trial that prolonged survival (9). The treatment with Ruxolitinib was performed between August 2014 and March 2017, and the therapy was well tolerated and the constitutional symptoms were controlled. The anemia, a side effect of Ruxolitinib, occurred during the first six months of treatment at Hb values of about 8.5 g/dL with a transfusion requirement at two months. The dimensions of the spleen were reduced in the first six months of treatment by 32.3%, from 19.2 cm at the start of the treatment to 13 cm, with the response maintenance.

After 20 months of treatment with Ruxolitinib, the patient had bilateral pulmonary thromboembolism that responded to the low-molecular-weight heparin treatment and required long-term anticoagulation.

In August 2016, 102 months after the diagnosis of myelofibrosis and 24 months after Ruxolitinib treatment, the patient was in partial remission with the hematological disease, according to the ELN criteria (13). However, the ultrasound examination, after CT, disclosed tumor formation on the right kidney with a diameter of 2.7/3/2.1 cm, with pulmonary metastasis. The reoccurrence of the clear cell carcinoma was confirmed based on the histopathological examination of the resected tumor on the right kidney at 44 months after the initial diagnosis. Optimally responding to Ruxolitinib treatment, the patient decided to continue the treatment. From an oncological point of view, the metastatic renal cell carcinoma would be treated with Sunitinib at the dose of 50 mg/day.

The combination of Ruxolitinib and Sunitinib, both with a medullary suppressor effect, induced pancytopenia with severe anemia requiring CER substitution treatment. The dose of Ruxolitinib was initially reduced, but

in March 2017, the treatment was interrupted due to severe thrombocytopenia. The renal carcinoma was evolving, with metastasis and required Sunitinib treatment. The anemia, determined by ineffective hematopoiesis and the medullary suppressor treatment, the upper gastrointestinal hemorrhage through coumarin overdose, required continued treatment with CER 2 units monthly and folic acid. The enhanced constitutional symptoms were attributed to the renal carcinoma rather than to myelofibrosis.

At the monitoring in March 2018, the patient was alive after 124 months of myelofibrosis and 64 months of renal carcinoma.

3. Discussion

The diagnosis of chronic myeloproliferative neoplasia, JAK2-negative idiopathic myelofibrosis, was established according to the WJO 2008 criteria by the patient meeting three major criteria and two minor criteria: megakaryocyte proliferation and reticulin fibrosis grade I/III in the medullary biopsy without significant morphological alterations for another myeloid neoplasm, without alterations in reactive fibrosis, leukoerythroblastic labels, and increased LDH. The diagnosis of idiopathic myelofibrosis was established at the age of 59 years, approximately 10 years earlier than the average age of the disease diagnosis reported in the literature (69 - 76 years).

The JAK2 mutation, a clonal marker of the idiopathic myelofibrosis, which is positive in 58% cases, was negative in this case. The genetic analysis of CALR and MPL mutations, which was negative, included the patient in the 10% cases with triple-negative idiopathic myelofibrosis (13).

The Lille score and subsequently the IPSS/DIPSS scores included the patient in the intermediate risk category 1, with a mean survival of approximately eight years (14). It should be noted that the prognostic scores in idiopathic myelofibrosis are calculated strictly based on the clinical-paraclinical parameters of the disease, without taking into account the comorbidities.

The initial treatment of the idiopathic myelofibrosis primarily aimed at controlling the proliferation: normalizing the platelet numbers with maintaining the spleen at approximately normal dimensions without transfusion requirements. This goal was achieved over a period of five years. The presence of constitutional symptoms (asthenia, weight loss, and nocturnal sweating) and progressive splenomegaly were the criteria for the initiation of treatment with Ruxolitinib. Ruxolitinib, as an inhibitor of Janus kinase, induces a significant improvement in the patient's quality of life, reduces the size of the splenomegaly, and decreases the death risk according to the COMFORT-II clinical trial. In the present case, Ruxolitinib at a daily dose of 20 mg twice a day could reduce the spleen size in the first three months of treatment, with a maximum effect in six months (32.3% reduction) and subsequent maintenance of the size; it controlled the constitutional symptoms and improved the patient's quality of life. The occurrence of anemia as a side effect commonly seen in patients treated with Ruxolitinib did not raise management problems, with the anemia being treated with CER (mean 2 UCER at three months).

The development of the thromboembolic event during the myelofibrosis treatment with Ruxolitinib is considered a complication associated with the two concomitant cancers rather than treatment with the tyrosine kinase inhibitor.

Treatment with Ruxolitinib was thought to be effective with achieving partial remission according to the WG-MRT (3) and ELN criteria. The stopping of Ruxolitinib after 37 months of treatment was required by the combination of Sunitinib for the treatment of recurrent renal cancer.

The emergence of second cancer in the fifth evolution year of the idiopathic myelofibrosis, as reported in the literature in 1.6% of the cases (10), raised concerns about patient's survival time. Nephrectomy is the standard therapy in the case of first-line renal cell carcinoma in Rosson stage I, which gives the patient a disease-free progression (renal carcinoma) of about four years; according to the literature, the survival rate was estimated at 66% in five years (8). The recurrence of renal carcinoma after nephrectomy, in stage IV with hepatic and pulmonary metastases, significantly contributed to the limitation of the hematological condition treatment, the stopping of Ruxolitinib and switching to Sunitinib. Sunitinib in metastatic renal cell carcinoma, as an RTK tyrosine kinase inhibitor, induces a disease-free survival of approximately 10.8 months with a global survival time of 30.4 months (15). Under Sunitinib treatment, the patient presented progressive disease with peritoneal carcinomatosis although idiopathic myelofibrosis was stable.

A strong point of this study is that the patient was diagnosed, treated, and monitored for primary myelofibrosis according to the European Leukemia Net.

3.1. Conclusions

We presented the case of a patient with triple-negative idiopathic myelofibrosis diagnosed at a young age with an intermediate prognostic score 1, which gave her a survival time of over eight years.

This case had a number of properties: the age of diagnosis (59 years), the association after five years of idiopathic myelofibrosis with second neoplasia, renal carci-

noma, the pulmonary thromboembolism, the partial response to Ruxolitinib, and the overall survival rate comparable with ones in clinical trials.

Footnotes

Conflict of Interests: The authors declare that they have no conflicts of interest.

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Patient Consent: The patient provided written informed consent for the publication.

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