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COVID-19 Hepatic Prodromal Syndrome in Patient with Non-Clear Cell Metastatic Renal Cell Carcinoma: A Case Report

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Abstract

Introduction: diagnostic and therapeutic difficulties for cancer are emerging in COVID-19 pandemic. In addition to interstitial pneumonia, disseminated intravascular coagulation and sepsis, liver injury (LI) is a fairly frequent occurrence, with significant weight on evolution and prognosis of COVID-19. Its involvement is linked to cholangiocytes ACE2. Excluded other pathogenesis, LI could represent prodromal phase of COVID-19, if initial diagnostic negativity will be followed by COVID-19 positivity.

Clinical case: A 59-year-old male patient has diagnosis of metastatic papillary non-clear cell renal cell carcinoma (nccRCC). After neoadjuvant Sunitinib he was submitted to right nephrectomy with caval-atrial thrombectomy in extra-corporeal circulation. Thereafter he continues Sunitinib until disease progression (PD) to bone followed by Axitinib from December 2015 to December 2015 and left femoral radiotherapy (RT) with disease control (DC). After lung and liver PD he was treated with Nivolumab from December 2015 to June 2016 with liver response and overall DC. After liver and caval thrombosis PD, Sorafenib, administered from June 2016 to December 2017, quarterly Zoledronic acid and bone RT obtained DC. Subsequent RT and Cabozantinib from February 2018 to September 2019, during which he reported pathological fracture of left femur, he underwent a surgical reduction and synthesis. From January 2020 to September 2020 Everolimus was administered with DC.

Subsequently, in light of PD related to immunosuppression, after proven COVID-19 negativity, he started therapy with intravenous low doses Cyclophosphamide, Fluorouracil and subcutaneous Interleukin-2 with moderate toxicity. Following the onset of dyspnea, confirmation of COVID-19 negativity, he was hospitalized and chest CT scan demonstrated size reduction of largest lung lesion. After antibiotic and steroid therapy with clinical improvement and discharge, patient complained symptoms worsening and biochemistry showed cholestatic hepatitis signs and INR lengthening. During subsequent hospitalization, he experienced rectorrhagia and biohumoral tests shown negativity for COVID-19, hypo-albumin, and persistence of coagulative and hepatic disorders. Change of immunological parameters, from which lymphocyte immunophenotype with initial increase of Treg counts followed by decrease during chemo-immunotherapy were observed. Despite support care, patient died with nasopharyngeal swab COVID-19 positivity.

Conclusion: This prodromal hepatic picture in heavy treated nccRCC could be an expression of increase of T lymphocytes and Treg counts, stimulated by IL-2, with negative feedback on hyper-inflammation, linked to hyper-cytokinemia, with attempt to control viral infection. It result in the delaying of the disease course whereas failure with lymphocyte and Treg reduction count culminates with final worsening until COVID-19 positivity.

Keywords: Renal carcinoma • COVID-19 • Interleukin-2 • Immune homeostasis • Liver injury

Introduction

After one year from the first case of COVID-19 reported in Wuhan, the capital of Hubei (China), on December 2019, on April 9th 2021 global cases and deaths are 133.146.550 and 2.888.530 respectively. We are currently going through the third pandemic wave and from COVID-19 vaccination campaign 669.248.795 vaccine doses are administered. Excluding the majority of cases presenting a mild SARS-CoV-2 infection, moderate and severe forms occur in 10%-20% of cases, symptomatic mainly following up into pneumonia which causes hypoxia and requires hospitalization. Severe forms are linked to hyper-inflammation and mainly result in acute respiratory distress syndrome (ARDS). It can be complicated by Disseminated Intravascular Coagulation (DIC) phenomena and septic shock, which require hospitalization in an intensive care unit, with a poor prognosis in about 2% of cases [1-3].

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However from other organ injury, liver involvement is frequent in patients who are COVID-19 positive. Liver injury (LI) is mostly often mild or moderate, whereas severe grade is present on among the 6.4% of patients, which is predictive of unfavorable disease course [4,5]. The frequent hepatic injury is related to the presence of ACE2 receptors, functional host receptor for SARS-CoV-2, especially in 60% of cholangiocytes whereas it has a minimal extent in hepatocytes and it is absent in Kuppfer cell [6]. In addition to hepatic toxicity linked to the drug administration for COVID-19 [7,8]. Varying degrees of hepatic involvement may present a higher rate of serum elevations of alanine aminotransferse (ALT). Mild liver involvement occurs in more than one-third of infected patients who can show elevated ALT or aspartate aminotransferase (AST), abnormal prothrombin time and low albumin level [9-11]. These serologic abnormalities are more frequent in COVID-19 positive patients than in negative patient ones [12,13]. Furthermore in positive patients, especially in those who have undergone auto transplantation or with primary liver cancer, their grade is related to the disease outcome, risk of complications, clinical worsening and the need for hospitalization in an intensive care unit and intubation [14]. Furthermore, a correlation between LI, use of drugs and its p possible negative impact on COVID-19 was found [15,16].

From the anatomo-pathological point of view, in the context of multi-organ involvement, LI is characterized by the presence of thrombi and neutrophilic plugs in the advanced stage of the disease, an expression of hyper-inflammation linked to IL-6 [17]. In the cancer patient, elevation of hepatic function indices can mainly be an expression of drug-related toxicity or hepatic progression. If these occurrences are excluded, this picture could

be defined as idiopathic. Another explanation could be the prodromal value of the clinical picture of a subsequent pathological manifestation of COVID-19. The purpose of this paper is to describe the therapeutic approach in a heavily pretreated patient with metastatic kidney cancer and to discuss the possible role of chemo-immunotherapy in warding off COVID-19 positivity after an intermediate phase of hepatic injury.

Case Description

Clinical case

A Caucasian 59-year-old male patient with previous duodenal ulcer, diverticulosis of the colon and sclerotic heart disease on past medical history, was recognized as having locally advanced neoplasia of the right kidney with atrial cavity thrombosis, pulmonary embolism and lung metastases. After renal biopsy, the diagnosis of clear and oxyphilic renal cell carcinoma with nuclear grade 4 according to Fuhrman classification was made. Its immunophenotypic profile was: $CK7^+$ (very rare elements), $racemase^+$, CD117-, $CAIX^+$ focal, EMA^+, $CD10^+$, Vimentina-, RCC^+ focal, CEA m^+ CEA m focal, A-Meltri-. From, June 2014 the patient underwent a neoadjuvant therapy with Sunitinib 50 mg/day for 28 days and repeated on day 42nd. After three cycles of therapy, as far as the size was concerned, the increase in size of large solid lesion to right kidney (about 19 × 17 × 16 cm) although with uneven density due to the presence of solid and large hypodense-necrotic colliquated component and bleeding suspect regarding peripheral mass in the perirenal space in correspondence of doubtful infiltration of ipsilateral psoas muscle was detected. Inferior vena cava, resulted unchanged, markedly ectasic (maximum caliber of about 55 mm) and occupied by thrombotic material, which extends into the thoracic tract of superior vena cava, with endocardiac involvement. There was an improvement of thromboembolic picture both in left renal vein and in the branch for the right lower pulmonary lobe. Bilateral lung nodules (up to about 13 mm) and hypervascular lesion to 2, 6 and 7 segments (S) of 8-18 mm of probable angiomatous appearance were stable.

Thereafter, he underwent a right nephrectomy with caval-atrial thrombectomy in extra-corporeal circulation and the pathological diagnosis was papillary variant of clear cell carcinoma pT3c pN0 according to WHO. Post-operatively treatment with Sunitinib was resumed for one cycle with stabilization. After PD to lungs and bone of left ischial tuberosity, recurrence of vena cava thrombosis and post-surgical outcome picture improvement, from December 2014 treatment with Axitinib 5 mg twice a day was then administered with disease control (DC). However on July 2015 bone scintigraphy showed areas of hypercaptation to lower right acetabular and ischio-pubic branch, and to lesser trochanter and the intertrochanteric region of left femur. This was confirmed by skeletal X-Ray, which showed a large osteolytic lesion of about 7 cm to left greater trochanter with extension to proximal shaft of the femur, and presence of reparative callus to right ischio-pubic branch, outcomes of doubtful pathological fracture. Radiotherapy 1300 cGy/2 fractions was performed and Axitinib was continued behind disease progression until December 2015 lacking of more effective alternative therapies and waiting for expanded access program with new agent anti-PD-1. After CT scan detection of liver PD on S1 (13 mm), S4 (15 mm), S5 (15 mm) e S6 (6 mm) and stabilization on lung nodal lesions and on extension of caval thrombosis of 7 cm × 3,5 cm, third line therapy with Nivolumab as compassionate use was delivered from December 2015 and performed until June 2016. Patient demonstrated good tolerance to therapy, obtaining stabilization to lung and nodal lesions and size reduction of liver metastases.

After PD on caval thrombosis which projects to atrial cavity, on liver mainly of two hypodense in S7, partially confluent, of 4.5 × 5 cm × 4,5 cm diameter and of hepatic hypodensity to S2 of about 2 cm, pulmonary thromboembolism recurrence, and stabilization on other sites of disease, Sorafenib 400 mg twice a day was administered from June 2016 to December 2017. During Sorafenib therapy an improvement of lung thromboembolism, low size reduction of liver metastases, and a stabilization of cavo-atrial thrombosis and lung lesions was detected. Radiotherapy (880 cGy/1 fr and 1000 cGy/2 fr) on right and left femur respectively stabilized bone metastatic lesions. From October 2017 Zoledronic acid 4 mg/3 months was administered for 4 times only for the onset of osteonecrosis of the jaw and was treated with sequestrectomy. After subsequent lung PD due to the appearance of 9 mm nodule in paraesophageal of right lower lobe, of two lymph nodes of 12 × 11 mm in left axillar, liver PD for increased S7 (30 mm vs. 17 mm) and progression of solid component of proximal meta-epiphyseal of the left femur (46 mm vs. 37 mm), he was treated with radiotherapy 1200 cGy/2 fr and Cabozantinib 60 mg/day from February 2018. After eight months, on October 2018 the patient reported pathological fracture of the subtrochanteric left femur and he underwent a surgery reduction and synthesis with PFN-A long intramedullary nail. Cabozantinib was administered until September 2019 for 19 cycles with a fair general DC. On September 2019 PD was detected due to the replacement of cavitated lesions in the right lung with areas of parenchymal consolidation (largest in apical segment of the upper lobe of 24 × 6 mm). Furthermore liver PD to S7 (40 mm diameter), increase of two hypodense oval retroperitoneal masses of about 22 × 16 mm, new appearance of soft tissue nodules to trunk of about 2 cm maximum diameter, bone progression on right ischio-pubic branch (50 × 34), on left proximal epiphysis of femur and stabilization in other sites, femoral re-irradiation (800 cGy/1 fr) and Everolimus 10 mg/day was administered from January 2020 to September 2020 with symptoms stabilization and moderate reduction in size of the nodules in the soft tissue of the trunk.

Subsequently, in light of the progression of predominantly pulmonary, hepatic and subcutaneous disease, after proven negativity of the nasopharyngeal swab for COVID-19, he started therapy with intravenous Cyclophosphamide 300 mg/m^2, Fluorouracil 500 mg/m^2 day 1 and low doses Interleukin (IL)-2 4.5 MUI subcutaneously day 3-6 and 17-20 every 4 weeks. During therapy he presented flu-like syndrome which regressed promptly after discontinuation of treatment. Following the onset of dyspnea, he went to the emergency room, where COVID-19 negativity was confirmed, and he was hospitalized for investigations and supportive care. Chest CT scan performed in suspicion of disease progression demonstrated a reduction in size of cavitated metastatic lung lesion and appearance of small new ones (Figures 1 and 2).

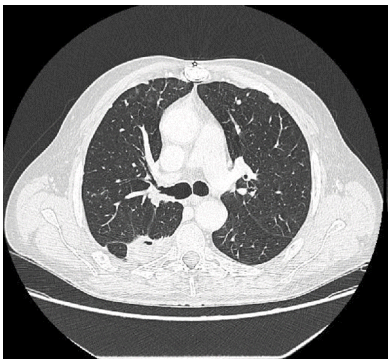

Figure 1. Presence of a cavitated lesion with more hypodense content of 30 × 28 mm at the upper segment of the lower right lobe.

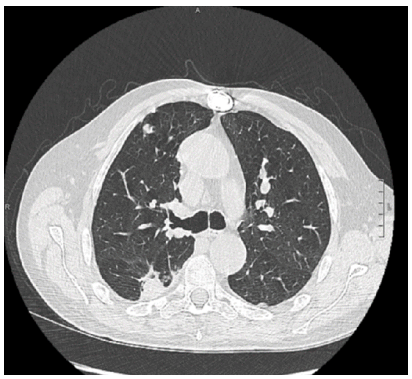

Figure 2. Size reduction of cavitated lung metastasis on upper segment of the lower right lobe and appearance of small new lesion.

After antibiotic and steroid therapy with clinical improvement, the patient was discharged. At a subsequent control visit, he complained asthenia, anorexia, pain in the right shoulder and on biochemistry serum elevation of ALT, AST, LDH, alkaline phosphatase, bilirubin and INR were highlighted (Figures 3 and 4). After persistence of the symptoms, appearance of acute retention of urine and worsening of pain in the right shoulder, he was hospitalized again after proved negativity of the nasopharyngeal swab for COVID-19. During hospitalization he experienced tachycardia, hypotension by haemorrhagic anemia due to rectorrhagia. Biohumoral tests shown persistence of INR lengthening and of cholestatic hepatitis picture and reduction level of albumin (Figures 3 and 4).

From a hematological point of view, following the immunophenotype trend during single cycle of chemo-immunotherapy, the initial increase in the $CD3^+$, $CD4^+$, $CD8^+$ and Treg cells count is highlighted with a marked reduction of B lymphocytes (Figures 5-7). This is followed by evidence of absolute monocytosis, eosinophilia and lymphocyte activation and normalization of T and B lymphocyte counts. After a few days it is followed by progressive decrease mostly in Tregs, $CD3^+$, $CD4^+$ and $CD8^+$ cells count and activation of neutrophilic granulocytes which ends with the positivity for COVID-19. Furthermore, increase of N/L ratio, decrease of P/L ratio and increase of PCR levels were observed (Figures 8-10). Despite discontinuation of cumarol therapy, plasma administration and blood transfusion, no clinical improvement was obtained. The patient died and the nasopharyngeal swab was positive for COVID-19.

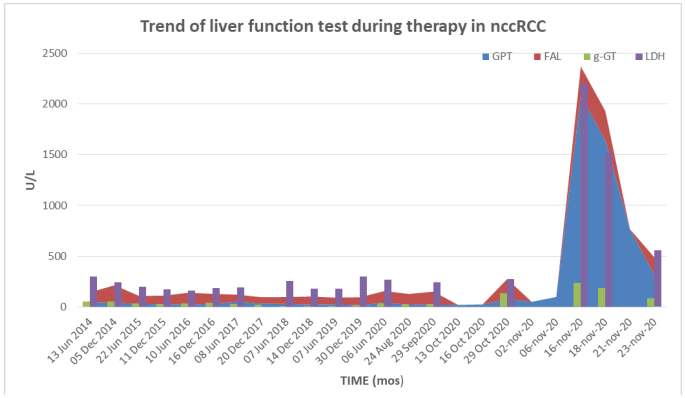

Figure 3. Trend of liver function test in non-clear cell renal cell carcinoma (nccRCC) during therapy: stability of the values of Glutamate-pyruvate transaminase or alanine aminotransferase (GPT), alkaline phosphatase (FAL), gamma-glutamyl- transpeptidase (g-GT) and lactate deydrogenase (LDH) from the beginning of the various therapies up to the suspension. Elevation of values in the last period during the negative phase of the test for COVID-19.

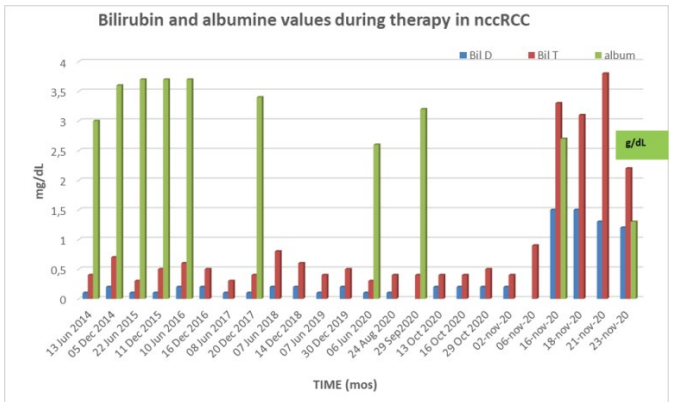

Figure 4. Trend of direct/total bilirubin (D/T Bil) and albumin (Album) in non-clear cell renal cell carcinoma (nccRCC) during therapy: stability of the values of D/T Bil and album from the beginning of the various therapies up to the suspension. Elevation of D/T Bil and decrease of album values in the last period during the negative phase of the test for COVID-19.

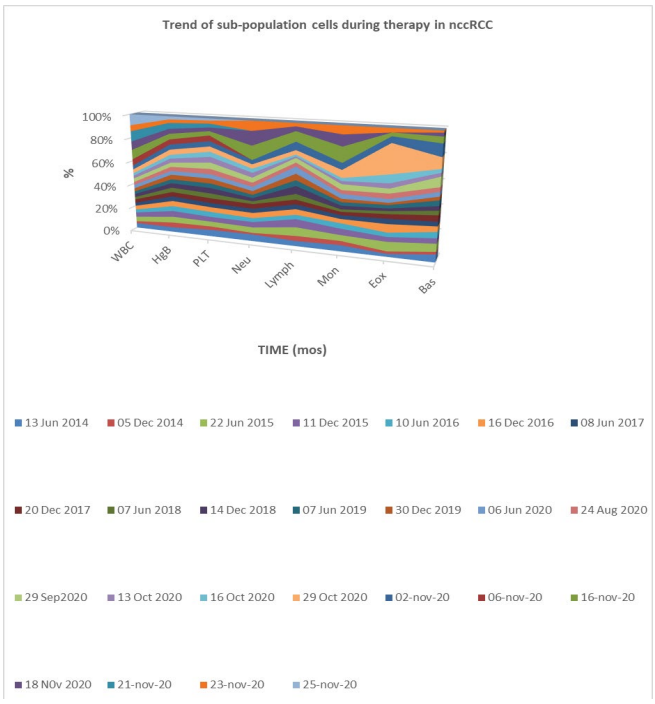

Figure 5. Trend of withe blood cell (WBC), Hemoglobin (HgB), platelets (PLT), neutrophil (Neu), lymphocyte (Lymph), monocyte (Mon), eosinophil (Eos) and basophil (Bas) in non-clear cell renal cell carcinoma (nccRCC) during therapy: stability of cell count during treatment with Tyrosine-kinase inhibitors except a slight increase in lymphocyte count. During the administration of mTOR inhibitor there is an increase in lymphocytes and eosinophils and a decrease in monocytes. This is followed by the stability of lymphocytes and monocytes and slow reduction of eosinophils.

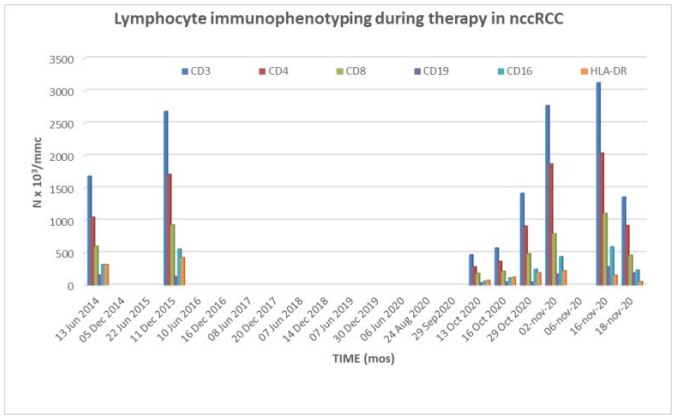

Figure 6. Trend of Lymphocyte immunophenotyping (co-receptor T cells ($CD3^+$), T helper cells ($CD4^+$), Cytotoxic and helper T cells ($CD8^+$), Natural Killer (CD16), B lymphocyte (CD19), Human leukocyte antigen, major histocompatibility complex of class II (HLA-DR) in non-clear cell renal cell carcinoma (nccRCC) during therapy: increase of cell count immunephenotyping during initial treatment with Tyrosine-kinase inhibitors. Subsequently in the last phase, after chemo-immunotherapy there is a progressive increase in the count of the various lymphocyte subpopulations which is followed by a decrease before the positivization for COVID-19.

Results and Discussion

The treatment of the cancer patient, whether for curative, adjuvant or palliative purposes, has slowed down during the COVID-19 pandemic. It has brought about changes in the clinical approach. COVID-19 disease is not only characterized by the well-known picture of pneumonia, but by other multi-organ involvement and LI is part of it. In neoplastic patient, signs of LI can be related to toxicities from systemic oncological treatment, especially in

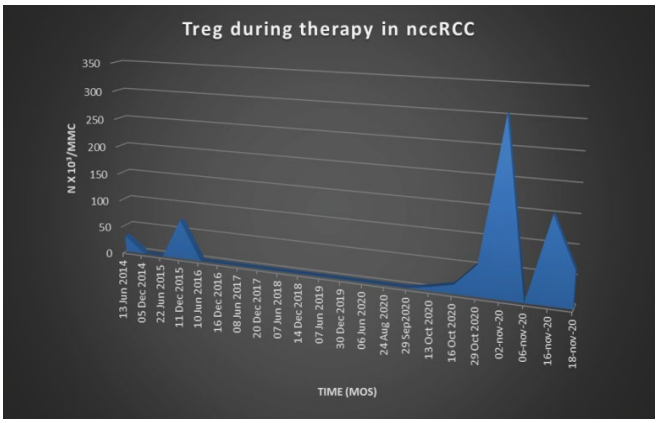

Figure 7. Trend of Lymphocyte T regulator (Treg) in non-clear cell renal cell carcinoma (nccRCC) during therapy: Increase of Treg count during initial treatment with Tyrosine-kinase inhibitors. Subsequently in the last phase, after chemo-immunotherapy there is a progressive increase in the count of Treg which is followed by a decrease before the positivization for COVID-19.

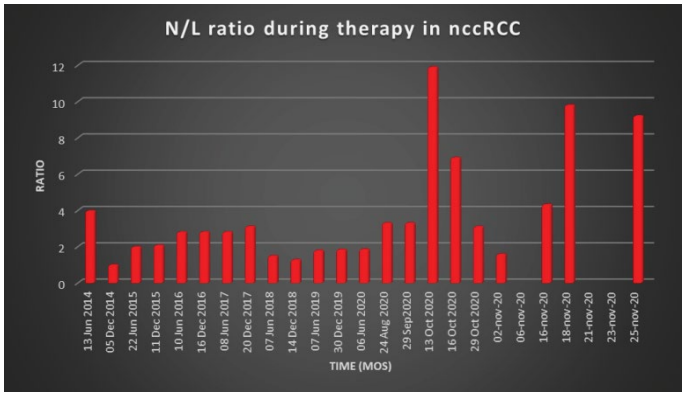

Figure 8. Trend of Neutrophil (N) Lymphocyte (L) ratio in non-clear cell renal cell carcinoma (nccRCC) during therapy: After an initial drastic decline of N/L ratio, there is a slow progressive increase followed by a further decrease. Subsequent increases of N/L ratio during mTOR inhibitor therapy that continues during chemo-immunotherapy, during which there is a reduction linked to an increase in lymphocyte counts. This is followed by a subsequent increase corresponding to lymphopenia before the positivization for COVID-19.

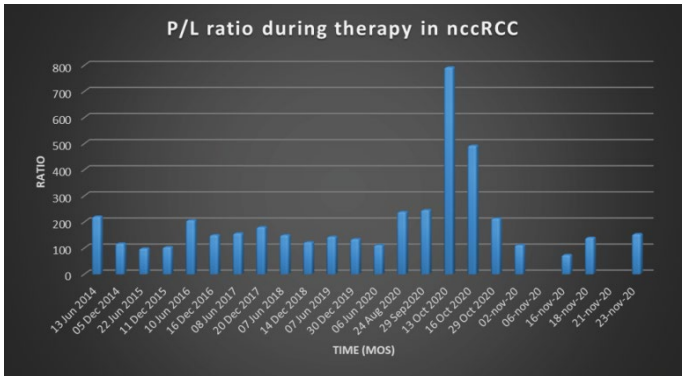

Figure 9. Trend of Platelets (P) Lymphocyte (L) ratio in non-clear cell renal cell carcinoma (nccRCC) during therapy: after an initial decline of P/L ratio, there is a slow progressive increase followed by a relative stationarity. After mTOR inhibitor therapy subsequent increases of P/L ratio is highlighted that continues during chemo-immunotherapy, during which there is a reduction linked to an increase in lymphocyte counts. This is followed by a subsequent increase corresponding to lymphopenia before the positivization for COVID-19.

conjunction with known comorbidities and all other conditions that may justify a particular framework must be excluded.

Regarding the last chemo-immunotherapy regimen used in a heavily pretreated patient, it does not justify the particular enzymatic elevations found after discontinuation of therapy [18,19]. Bio-humoral hepatic picture cannot be explained by the mere presence of metastases since the cholestasis indices were not elevated previously (Figure 3). Therefore, after carrying out investigations aimed at confirming or not the possible etiopathogenesis of the hepatic injury, in light that patient was in incubation period of COVID-19, the prodromal character of picture must be taken into consideration. In physiological conditions, the production of type I interferon represents the first line of defense responsible for blocking and destroying the virus after its recognition by the receptor for the pathogen (PRR) and the interaction with the specific Pathogen-Associated Molecular Pattern (PAMPs) [20].

It follows activation of innate and adaptive immune system through Damage Associated Molecular Patterns (DAMP) released by damaged or dying cells [21,22]. However, this defense mechanism can promote a pathological inflammatory response with stimulation of innate T cell and lymphopenia. Furthermore, in the course of the disease, especially in severe forms an increase in monocytes and macrophages is responsible for high levels of pro-inflammatory cytokines which in some patients are the so-called cytokine storms, often associated with a poor outcome. A certain inhomogeneity of the various cytokines can be found in the various forms of COVID-19 disease. In fact, in the moderate and high severity forms are present IL-1α, IL-1β, IL-17A, IL-12 p70, and IFNα while in severe forms other inflammatory clusters are detected thrombopoietin (TPO), IL-33, IL-16, IL-21, IL-23, IFNλ, eotaxin and eotaxin 3, IL-6, IL-10, IL-18 and TNF. In moderate forms they can undergo a decline within 10 days differently from patients with severe forms which are characterized by a prolonged duration. This results in a progressive reduction of type 1 (antiviral) and type 3 (antifungal) responses with concomitant increase of IL-5, IL-13, immunoglobulin E and eosinophils [23]. Comorbidities such as old age, cardiovascular disease, renal failure, hypertension and male sex can worsen the clinical picture.

Physiologically, the maintenance of immune homeostasis is the result of balance between two opposite mechanisms. The hyper-inflammatory response of the cytokine storm is opposed by type B and T regulatory (reg) lymphocytes, myelo-derived suppressor cells, regulatory dendritic cells and the cytokines IL-4, IL-10, IL-25 and TGF which perform an inhibitory action on the immune response for the maintenance of homeostasis [24]. In case of viral infection, due to SARS-CoV2, it seems that the lowering of the homeostatic and regulatory phase is decisive for the prevalence of the pro-inflammatory phase.

A possible explanation for this imbalance is given to a lower antiviral transcriptional response represented by low levels of IFN-I and IFN-III and a high expression of chemokines, which translate in the pro-inflammatory response typical of COVID-19, especially in the elderly population differently

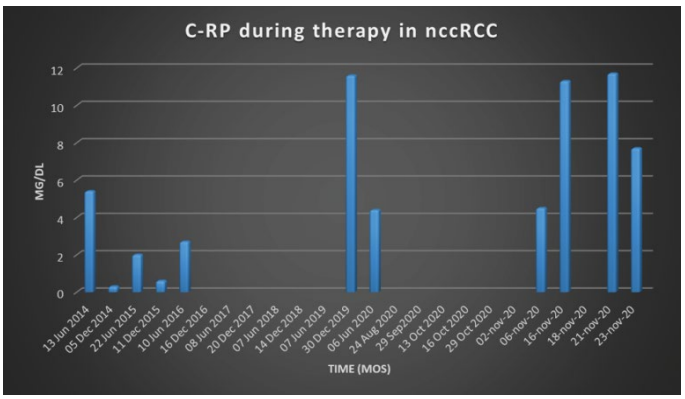

Figure 10. Trend of C-reactive protein (C-RP) in non-clear cell renal cell carcinoma (nccRCC) during therapy: After an initial decline of C-RP, there is a slow progressive increase followed by rapid increases after mTOR inhibitor therapy. During chemo-immunotherapy there is a reduction linked to an increase in lymphocyte counts. This is followed by a subsequent increase corresponding to lymphopenia before the positivization for COVID-19.

from the young patients [25,26]. Another explanation of reduction levels of type I interferon is the autoimmune one. It is more present in the elderly subjects than in the young ones and this would explain the different clinical trend in the different patient populations [27]. Finally, the increase in IL-2 and IL-7 seen in COVID-19 patients probably represents an attempt by the immune system to reverse lymphopenia and T cell depletion, respectively [28]. The action mechanism of IL-2 is also exerted on Treg with the role of inhibiting excessive inflammation and contributing to the repair of lung damage. In fact, this occurs when the function of Treg cells is reduced or diminished [29].

This immune-pathogenic mechanism of COVID-19 emphasizes the possible importance of IL-2 administration. The purpose of the chemo-immunotherapy combination was to exploit the immunosuppressive effect of Cyclophosphamide on Tregs and of Fluorouracil on MDSC, putting IL-2 in the best conditions to exercise a more prompt immune stimulation. However, this effect is dynamic and can be followed by a rebound of the immunosuppressive cells with a possible influence of the IL-2 dose used, and the time of administration [19,30]. Since SARS-CoV-2 infection has been associated with depletion of cytotoxic lymphocytes, ultra-low doses of IL-2 are able to rebalance the immune response through the stimulation of Tregs [31-34]. This effect could counteract the state of autoimmunity and allow the regression from the state of exhaustion of lymphocytes, counterbalancing the appearance and the inexorable course of the cytokine storm.

Furthermore, in the light of the rare thrombotic complications post-vaccine COVID-19 with autoimmune etiology, similar to those secondary to heparin administration, a possible further role in favor of IL-2, due to its autoimmune inhibitory action, could be identified [35,36]. The long natural history of our heavily pretreated patient with an unfavorable histotype can be correlated to the stable immune status over time in line with the C reactive protein trend, to the good organ tolerance, mainly hepatic, of the treatments used (Figures 3 and 10). Furthermore it is interesting the correlation of the breakdown of the immune balance with the period of treatment with Everolimus, which possesses immunosuppressive activity (Figure 10). Noteworthy is the early and unexpected sign of response to chemo-immunotherapy in light of heavy pretreatment and the unfavorable histotype of renal cell carcinoma.

Conclusion

It is worth noting how the immunophenotype trend during the single course of chemo-immunotherapy, with an initial increase in the $CD3^+$, $CD4^+$, $CD8^+$ and Treg cell counts, is followed by lymphocyte activation and how the hyperinflammation follows the subsequent decrease mainly of Tregs, CD3+, $CD4^+$ and $CD8^+$ cell counts. In conclusion, this prodromal hepatic picture, above quoted, could be an expression of the negative feedback due to the increase of regulatory T lymphocytes, stimulated by IL-2, on hyper-inflammation linked to hyper-cytokinemia with attempt to control and counter viral infection and resulting in the delaying of the disease course culminating with final worsening until COVID-19 positivity. This is a hypothesis generating a further study aiming to be proved, prospectively, on an adequate cohort of cancer patient with the support of the immunophenotype, cytokine and metabolomic profile.

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