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CASE REPORT

COVID-19 infection in a patient with Follicular non-Hodgkin Lymphoma. A Case Report

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Abstract

Follicular non-Hodgkin Lymphoma (FNHL) is the most common type of indolent non- Hodgkin Lymphomas (NHL) that develops from abnormal B lymphocyte that form follicle-like clusters inside the lymph nodes (1). The prevalence of FNHL is estimated around 1 in 3000 patients, being usually encountered in elderly, 60 years old patients and diagnosed in advanced stages when monoclonal antibodies alone or combined with other chemotherapy agents are needed (2).

Recent studies about COVID-19 infection prognosis suggest that oncologic patients are at high risk of morbidity and mortality due to SARS-CoV-2 infection, partially because of the secondary immune deficiency due to malignant pathology itself but also to the accumulated

toxicity secondary to the immuno-chemotherapy treatment. (3).
This case report describes a young female patient with FNHL with Bulky abdominal tumoral mass detected at CT scan, in Complete Remission after immune-chemotherapy treatment, contacting COVID-19 twice, first in 2020 and second time in 2022. Even if the patient has been vaccinated against SARS-CoV-2 in late 2021, she did not develop an increased titer of either SPIKE anti-protein neutralizing antibodies (Protein S) or anti- Nucleocapsid IgG antibodies.
***Keywords**: follicular non-Hodgkin lymphoma, immuno-chemotherapy treatment, COVID-19.*

Case presentation

A 44-year-old woman was addressed in late 2017 to Otorhinolaryngology Department of Emergency Municipal Hospital from Timisoara with multiple submandibular, retro-auricular, latero-cervical, axillary and inguinal lymphadenopathies. She also reported mild asthenia and fatigue but denied fever, chills, sweats, or pruritus. From the past medical history, it appeared that the patient had meningitides and vertigo syndrome, but the family history was not contributory. The patient did not follow any previous medical treatment.

A biopsy from the right later- cervi lymphadenopathy was performed and based on Histopathological and Immunohistochemical Exam the diagnosis of Follicular Non-Hodgkin Lymphoma with B cells, grade 1-2, CD20+ was established. Following diagnosis, the patient was directed towards Hematology Department of Emergency Municipal Hospital Timisoara.

At the objective examination the patient presented mildly pale-jaundice skin, and submandibular, retro-auricular, latero-cervical, axillary, and inguinal lymphadenopathy. No signs of pulmonary, cardiac, digestive, renal, neuronal abnormalities were found.

Laboratory investigations showed a folic acid deficiency, a rise concentration of D-dimer, and C Reactive Protein (CRP) and Helicobacter pylori infection: Folic Acid =3.58 ng/ml, D- dimer = 944 ng/ml CRP=2mg/L. The complete blood count and coagulation tests were normal - White Blood Cells (WBC) = 7.67*103/▫L, Hemoglobin (HBC) = 14.0 g/dl, Platelets (PLT)=266*103/▫L, APTT = 28.7sec, PT = 11.9 sec, INR = 1.10.

For staging the lymphoma, multiple paraclinical investigations were performed. The Hip Medullary Aspirate showed a normal count of lymphocyte (15%) and the presence of rare abnormal lymphocyte (1%).

Osteomedullary Biopsy was performed and in the biopsy specimen medullary lymphoid infiltration with diffuse B-positive cells was found. The Immunohistochemistry was undertaken and was positive for CD20 and PAX5 expressing BCL6 (centrofollicular B marker) in frequent cells; The Histopathological aspect and Immunophenotypic configuration suggests a medullary infiltration of approximately 30-35% of malignant Follicular Non- Hodgkin Lymphoma with B cells, grade 1-2.

Cervical, Chest, Abdominal and Pelvic CT scan was performed, which detected the presence of an abdominal- pelvic mass with bilateral ureteral compression, stage 1 ureterohydronephrosis
and multiple submandibular, retroauricular, latero- cervical, axillary and inguinal lymphadenopathies.

Based on the anamnestic, clinical and paraclinical data the diagnosis of FNHL with B cells, 1-2 grade, CD20+, Stage IVBX was established.

An enrollment of the patient in a clinical trial for FNHL was attempted, however, due to the 4 region CT scan that showed the Bulky abdominal mass it was considered screening failure.

On 29th January 2018 the first application of Immuno-chemotherapy induction treatment was advised by the Hematologist; the treatment being advised in a total of 8 cycles administered according to European Society of Medical Oncology (ESMO) protocol. The treatment regimen followed was R-CHOP which comprised of using Rituximab, Cyclophosphamide, Doxorubicin (Hydrodoxorubicin), Vincristine (Oncovin) and Prednisolone.

The patient was examined every 3 weeks, at every admission during induction treatment. The Immuno- chemotherapeutic treatment was well tolerated, being associated at each Immuno-chemotherapy application hydro- electrolytic rebalancing treatment, gastroprotective, hepatotropic, antibiotic, antiemetic and analgesic treatment.

At the end of 3 complete cycles the FNHL was considered partial remission and at the end of the 8 cycles, based on the PET-CT scan performed and it was considered complete remission.

On 29th August 2018 maintenance treatment with anti CD20 monoclonal antibody, Rituximab was initiated. The evolution was favorable, patient having a good general condition and no sign of recurrence. In total, 11 applications of Rituximab were administered.

On 3rd December 2020, the patient was admitted in the COVID Department of Emergency Municipal Hospital from Timisoara trough Emergency Department (ER) for worsening fatigue, dyspnea, chills and fever that does not yield to antipyretic treatment, anosmia, myalgia, insomnia, loss of appetite, and constipation alternating with diarrhea. The patient had history of positive RT-PCR-SARS-COV-2 tests since 29th October 2020, initially underwent specific treatment at home, but the symptoms worsened in the past 14 days before the ER presentation.

At the Physical exam the patient had blood pressure (BP)=106/61mmHg, heart rate (HR)= 89bpm, temperature=37.6C, SaO2=95% spontaneous, with no sign of cyanosis and no sign of respiratory failure. No other pathological signs were observed. At the admission the laboratory investigations showed mild anemia and leukopenia with neutropenia–WBC 2.32*103/¤L, Neutrophils=1.36103/¤L, HBG=10.6g/dl, but after one week the patient developed leukocytosis, mild hyponatremia, mild hyperpotassemia, acute cytolysis syndrome and increased inflammatory markers WBC=11.56103/¤L, GOT=159U/L, GPT=51 U/L, Na=130mEq/L, K=4mEq/L, erythrocyte sedimentation rate (ESR)=30mm/h, CRP=25mg/L, Fibrinogen =500mg/dl, D- dimer=1348.8ng/ml, Ferritin=2701.36ng/ml.

A chest CT scan in which discrete areas of ground-glass in both lung fields were detected, with lung damage under 20%, associated with fine pleuro- pericardial fluid effusion.

On 11th December 2020, after one week hospitalization, fungal examination of sputum developed micro- and macroscopic aspect of Aspergillus infection.

The RT-PCR-SARS-COV2 retest in 16th and 18th December 2020 were positive.

During hospitalization the patient presented oscillating fever under antipyretics and oxygen desaturation which is why oxygen mask was needed.

The evolution was unstable in the first days, with a subsequent improvement of the clinical condition under specific treatment with antibiotics-Ceftriaxone 2g/day, Moxifloxacin 400mg/day, Meropenem 3g/day, antifungal-Fluconazole 200mg/day, antivirals-Remdesivir 100mg, for 5 days antipyretics–Paracetamol 1g/day, gastric protection-Famotidine 40mg, vitamins-C vitamin 1,5g/day, D vitamin 5000UI/day, anticoagulants-Clexane 2x0.6ml/day, and corticosteroids Dexamethasone 8mg/day, and the patient was discharged in 21.12.2020, after 18 days of hospitalization.

On 28th December 2020 the general condition of the patient worsened and she was once again admitted in the COVID Department of Emergency Municipal Hospital from Timisoara through ER with influenced general condition, severe fatigue, sweats, chills, cough and moderate dysphagia. At the Physical exam the patient had BP=100/60mmHg, HR=11bpm, temperature=38.7C, SaO2=97% spontaneous.

No other pathological signs wereobserved.

The RT-PCR-SARS-CoV2 test performed on 5th January 2021 was still positive.

During 28th-31st December 2020 antibiotic treatment–Piperacillin/Tazobactam 4 ampoules/day, Linezolid 600mg twice a day, antifungal treatment-Voriconazole 200mg twice a day, Capsofungin 50mg daily was administered. On 1st January 2021 antibiotic treatment was reconsidered, Meropenem 3g/day being initiated. From 7th January 2020 Tigecycline 50mg/day, Micafungin 100mg/day was initiated. During hospitalization Intravenous Immunoglobulin, antipyretic and hydro- electrolytic treatment was associated.

The evolution was slowly favorable, and the patient was discharged on 24th January 2021, after 27 days of hospitalization.

It is mentioned that the maintenance treatment with Rituximab was discontinued due to the COVID-19 infection, 11 applications being administered.

On 4th March and 16th April 2021 patient was addressed to the Hematology Clinic for reevaluation, each time Intravenous Immunoglobulin treatment being administered.

The patient had 2 vaccine doses against SARS-CoV2 in late 2021. SPIKE anti-protein neutralizing antibodies (Protein S) and anti-Nucleocapsid IgG antibodies were subsequently dosed, but the titer was low, suggesting that the patient did not develop protection against SARS-CoV-2 infection.

On 17th February 2022 patient was once again positive for COVID-19 infection. Even though the antibody titer was low, this time she had mild symptomatology, experienced headache, nausea, rhinorrhea, cough, sore throat and mild fever (37.8C). Hospitalization was not needed, evolution was favorable under antiviral treatment with Molnupiravir and antibiotic treatment with Cefixime, followed at home.

Currently, the patient has a good general condition, progression-free, with no signs of relapse of FNHL.

Discussions

Majority of malignant lymphomas could be divided into two groups – Hodgkin Lymphomas (HL) and non- Hodgkin Lymphomas (NHL), based on the microscopic histologically presence/absence of the multinucleate Sternberg-Reed cells (4). There are over 60 types of NHL but based on the growth rate of the abnormal lymphocytes, NHL could be divided in turn into High-Grade non-Hodgkin Lymphomas (HGNHL), or aggressive lymphomas and Low-Grade non-Hodgkin Lymphomas (LGNHL), or indolent lymphomas. FNHL is the most common type of LGNHL and is developed from abnormal B cells that form follicle-like clusters inside the lymph nodes.

FNHL B symptoms, such as sweating, chills, mild fever, fatigue, associated with painless enlarged lymph nodes are nonspecific (6), which is why they are mainly diagnosed in advanced stages. In early stages, watch and wait or radiotherapy could be the preferred treatment options, but in advanced stages chemotherapy protocols are needed (5).

In the case presented the patient was diagnosed in an advanced stage, as FNHL with B cells, 1-2 grade +, Stage IV BX. The Follicular Lymphoma International Prognostic Index (FLIPI) has been calculated by assessing one point to each criterion: age above 60 years old, hemoglobin level below 12g/dl, serum lactate dehydrogenase above normal, stage III-IV of NHFL at the diagnosis and more than 4 lymph nodes affected. A higher FLIPI score was associated with an increased risk of morbidity and mortality (7). The presented patient had a FLIPI score of 2, which means that the patient was considered in intermediate risk class.

It is well known that oncologic patients are at high risk of developing an infectious disease associated with an increased risk of morbidity and mortality in case of an infection.

Since the beginning of COVID-19 pandemic, studies tried to identify the group of patients that are at high risk of developing severe complications and death due to SARS-Cov-2 infection. Lymphoma patients appeared particularly vulnerable to COVID-19, partially because of the secondary immune deficiency due to malignant pathology itself, but also to the chemotherapy treatment (3,8).

The case presented an FNHL patient that responded well to specific treatment with 8

R-CHOP applications that led to coplete remission followed by maintenancei mmunotherapy with 11 Rituximab applications. SARS-CoV-2 infection had initially an unfavorable evolution which may be due to the toxicity accumulated after chemotheapy.

Conclusions

FNHL is an indolent type of non- Hodgkin Lymphoma that usually affects the elderly population. FLNH patients have an average age of 63.5 years, only 4% being around 40 years old or younger (9).

Even though, the case presented a young patient aged 40 years at the time of diagnosis with an intermediate score risk, with a 10-year survivance rate above 50%, who acquired complete remission after immunochemotherapy treatment, SARS-CoV-2 infection initially had an unfavorable evolution.

The invasive fungal pulmonary infection with Aspergillosis could be reported as a nosocomial infection secondary to prolonged hospitalization but also to a weakened immune system. RT-PCR-SARS-CoV-2 tests remained positive from October 2020 till January 2021, period in which patient needed over 40 days of hospitalization. Additionally, patient had COVID-19 once again at the beginning of 2022, but this time the evolution was quickly favorable. Even though the titer of antibodies against SARS-CoV-2 was low, considering that the patient had 2 vaccine doses prior to the second COVID- 19 infection which was defined by a mild symptomatology with no hospitalization period needed, the importance of vaccination prophylaxis is suggested.

In conclusion, SARS-CoV-2 infection could have a serious outcome in oncologic patients which is why extra precautions measures against infections are needed.

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