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Case Report

Internal Medicine Section

Diffuse Large B-cell Lymphoma-Treatment Failure, Recovery and COVID-19: A Case Report

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ABSTRACT

Diffuse Large B-cell Lymphoma (DLBCL) is the most common form of non-hodgkin lymphoma, involving multiple organ system including lymph node, bone marrow, spleen etc. Among overall cases of DLBCL, 40% are extranodal in origin and stomach being the most common site. While most of the (60%) are not diagnosed until the disease reach stage 3 or 4. While in the present case of a 65-year-old female, patient had predominant involvement of neck lymph nodes. Following the final diagnosis, patient was given first line treatment in the form of Rituximab, Cyclophosphamide, Hydroxydaunorubicin hydrochloride (doxorubicin hydrochloride), vincristine (Oncovin) and Prednisone (R-CHOP) regimen, to which patient didn't respond and further the patient was given Rituximab, Ifosfamide, Carboplatin, and Etoposide (R-ICE) regimen, to which patient responded quickly. With Coronavirus Disease 2019 (COVID-19) pandemic, the patient encountered infection with its associated complication. The following case report is all about the timely management of DLBCL and patient's survival with COVID-19 and its related complication. Haematological malignancy such as lymphomas, leukaemias, myelomas cause severe myelosuppression and lymphodepletion increasing the risk for development of COVID-19. Studies have shown that patients with malignancy had an estimated two-fold increased risk of contracting Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) than the general population. The survival rates strongly depend on COVID-19 stage and other factors such as immune (neutropenia) status and systemic inflammation.

Keywords: Chemotherapy, Coronavirus disease-2019, Haematological malignancy, Lymphoma, Non-hodgkin lymphoma

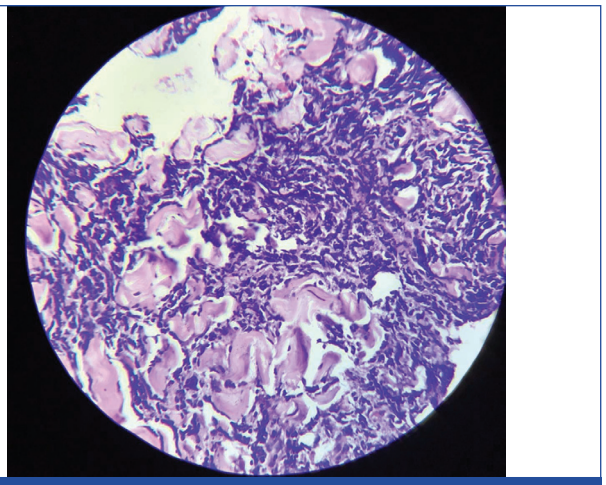
CASE REPORT

A 65-year-old female was brought to the Emergency Department with a complaint of right side neck swelling for three months and constitutional symptoms like a low-grade fever, decreased appetite, weight loss around 8-10 kg in last six months. The subject had no other underlying co-morbidity including diabetes and hypertension. While on a detailed history, she didn't have a previous history of viral infection, drug allergies, drug intake or addictions.

On examination, there were multiple discrete swellings noted largest measuring approximately 2×2 cm with ulcerations and serous discharge, while no other lymph nodes palpable clinically. Patient was later subjected to laboratory investigations as shown in [Table/Fig-1] and ultrasound of neck which showed multiple hypoechoic lymph nodes of size 1-2 cm at level II-IV and submandibular region suggestive of neoplastic aetiology. Considering the fact as revealed in ultrasound that patient was suffering from underlying malignancy, she was referred to onco-physician and was advised Fine Needle Aspiration Cytology (FNAC) and excisional biopsy and immunohistochemistry. The FNAC of right cervical lymph node (1st initial biopsy) showed Non-hodgkin's lymphoma, excisional biopsy of right cervical lymph node showed proliferation of large lymphoid cells, with elongated, pleomorphic, and prominent nucleoli along with few scattered small lymphocytes [Table/Fig-2]. Immunohistochemistry showed neoplastic lymphoid cells which were strongly positive for CD45, CD20, CD10, Bcl2 and Bcl6 and negative for Pan CK, HMB 45 and C3. Ki-67 index was 65 percent. The findings were consistent with primary cutaneous DLBCL.

Laboratory investigations	Patient	Normal value
Haemoglobin (gm%)	12.20	13.5-18
Total Leucocyte Count (TLC) (/µL)	10900	4000-11000
Platelet count (µL)	249000	150000-450000
Total bilirubin (mg/dL)	0.30	0.1-1.2
Direct/indirect (mg/dL)	0.06/0.24	0.1-0.3 / 0.1-1.0
SGOT/SGPT (U/L)	25/10	5-36/ 5-41
Alkaline phosphatase (U/L)	115	40-129
Total protein (g/dL)	6.81	6.6-8.7
Albumin/globulin (g/dL)	3.37/3.44	3.5-5.2/2-3.5
Urea (mg/dL)	19	5-20
Creatinine (g/dL)	0.81	0.5-1.3
Urine Routine/microscopy	WNL	-

[Table/Fig-1]: Laboratory values.
SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; WNL: Within normal limits

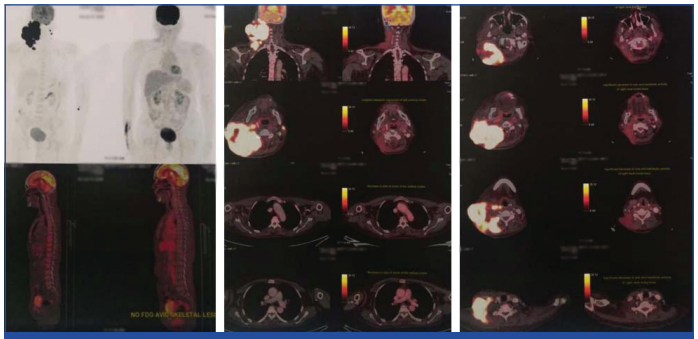


[Table/Fig-2]: Light microscopic view of HPE section of lymph node- Photomicrograph shows diffuse large lymphoid cells with high grade pleomorphism and mitosis; also seen are small lymphocytes (H&E,100X).

Along with the available investigation, patient was referred to oncologist and the working diagnosis of primary cutaneous DLBCL was made and the patient was advised chemotherapy. Prior to the investigations all laboratory investigations were repeated which were consistent with previous ones.

The echocardiography and electrocardiogram study was within normal limits prior to the initiation of chemotherapy.

Four cycles of chemotherapy regimen (R-CHOP regimen) were administered uneventfully, but no significant improvement was noted suggesting the treatment failure. An expert opinion of oncologist was sought, who opined that patient must undergo PET scan study [Table/Fig-3] which showed hypermetabolic bulky right neck nodal mass. Hypermetabolic bilateral cervical nodes. Low grade metabolic activity seen in bilateral axillary, internal mammary and left abdominopelvic nodes. The above scan was performed after the fourth chemo, suggesting the treatment failure.



[Table/Fig-3]: PET Scan Images showing the significant improvement from 1st cycle R-ICE regimen of chemo to the last cycle.

Repeat biopsy showed neoplastic lymphoid cells showing strong diffuse positivity for CD20, CD10, Bcl-2 and Bcl-6 while they were negative for MUM-1 and C-MYC (20%). MiB-1 labelling index is high (70%). Diffuse large B cell Lymphoma involving skin-germinal center B-cell (GCB type: Hans Algorithm) was observed.

The Oncologist, considering the treatment failure, decided to modify the further cycles of chemotherapy as:

Cycle 5: R-ICE regime-Rituximab (500 mg)+ICE regime given to which patient responded, the swelling size was on the decreasing trend.

Cycle 6: R-ICE regime-Rituximab (500 mg)+ICE regime given to which patient responded and substantial decrease in the size was noted in next few weeks.

Following the sixth cycle completion patient started responding clinically and was discharged with the nursing care and was asked to follow-up for seventh cycle of chemotherapy. Eighteenth day following the seventh cycle of chemotherapy, patient developed fever with chills along with the dry cough. Considering the possibility of COVID-19, the swab was sent for Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) which turned out to be positive and she was started on the following treatment and further cycles of chemo was deferred as advised by oncologist. [Table/Fig-4] shows the levels of inflammatory markers on third and 21st day of COVID-19. The treatment advice for COVID-19 is outlined in [Table/Fig-5].

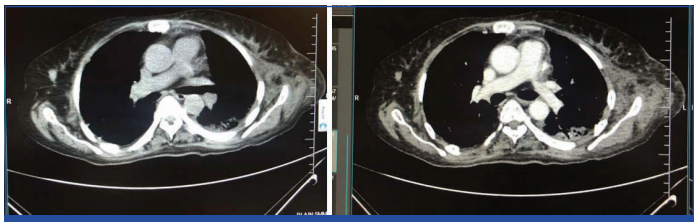
Inflammatory markers	3rd day of COVID-19 illness	Post 21 days of COVID-19 illness
D-dimer (ng/mL)	>10000	632
C-Reactive protein (IU/mL)	298	10
Erythrocyte sedimentation rate (mm/hr)	87	56
Ferritin (µ/L)	462	350
Interleukin-6 (pg/mL)	150	7
Lactate dehydrogenase (IU/L)	788	522
Procalcitonin (ng/mL)	101	<0.3

[Table/Fig-4]: Inflammatory markers on days 3 and 21 of COVID-19.

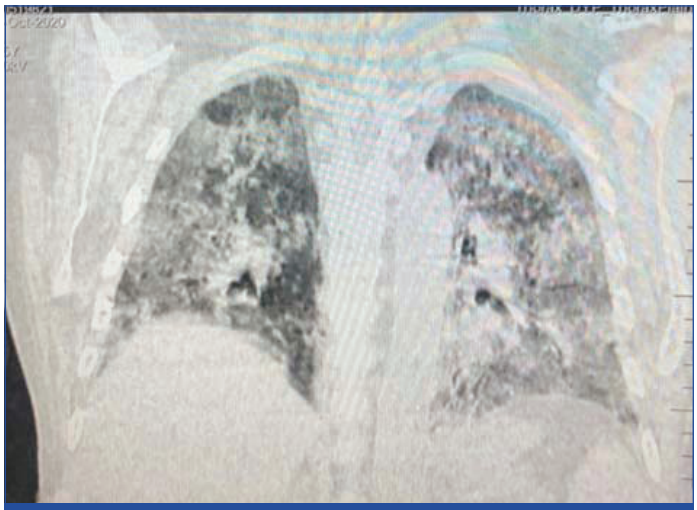
Injection	Dose
Inj. Dexamethasone 8 mg	TDS for 7 days i.v and tapered
Inj. Enoxaparin 0.6	BD S.C for 14 days
Tab Rivaroxaban 20 mg	(overlapped for 5 days with parentral anticoagulant) OD orally after food further dose was tapered
Inj. Remdesivir	200 mg Day 1 stat dose Followed by 100 mg Day 2-Day 5
Inj. Imipenem and Cilastin 1 gm	BD i.v for 14 days
Inj. Metronidazole 100 mg	TDS i.v for 14 days

[Table/Fig-5]: Treatment of COVID-19 Pneumonitis.

On third day of COVID-19 illness, the subject developed sudden onset of breathlessness and unexplained tachycardia, while ECG was substantiating only sinus tachycardia. While taking into account the malignancy induced hypercoagulable state and prothrombotic nature of COVID-19 illness and considering the possibility of pulmonary embolism, patient underwent various investigations including inflammatory markers as depicted in [Table/Fig-4] and CT Pulmonary-Angio [Table/Fig-6], which revealed partial filling defect in bilateral posterior basal and right side lateral basal arteries and distal branches suggesting thrombosis and Computed Tomography (CT) severity index was 24/25. Other radiographic and clinical pictures are provided in the [Table/Fig-7,8].



[Table/Fig-6]: CT pulmonary angio graphy images suggestive of Pulmonary emembolism.



[Table/Fig-7]: HRCT Image: Depecting diffuse ground glass opacities fields, CT score 24/25.

[Table/Fig-8]: Images of the clinical improvement.

On day 8 of illness, patient was weaned off from oxygen support and was shifted to normal ward. As the patient was immunocompromised due to pre-existing DLBCL and underlying COVID-19, the eighth cycle of chemotheraphy was deferred for next three months and the decision was completely subjective, and was taken by the panel of oncologist considering the risk of chemotherapy induced complication versus its benefit in the current situation. Further she

was discharged on Pirfenidone and Rivaroxaban. Currently the patient is under follow-up and next four cycles of chemotherapy has been administered successfully.

DISCUSSION

Herein reporting a case of Diffuse Large B-cell lymphoma (DLBCL) which is the most common histologic subtype of NHL complicated with COVID-19 pneumonitis and Acute Pulmonary Thromboembolism. Median age at diagnosis is 70 years [1,2]. While patients like this who presents as a cervical lymph node enlargement in developing country like India, the first differential diagnosis would be tubercular lymphadenitis/cold abscess while in western countries it will mostly be lymphoma. However, other differential diagnoses comprise of infectious mononucleosis, Hodgkin, T-cell mediated lymphomas. Similarly, other malignancies such as carcinomas, melanoma, and Kikuchi disease can also be considered. When melanomas are considered as differential, it can be differentiated from DLBCL by (+) S100, HMB-45 and Melan A Staining. Therefore, urgent investigation and biopsy is indicated to confirm the final diagnosis. [3,4,5]

While in current scenario DLBCL was established as final diagnosis on HPE. The DLBCL peculiarly appraise diffuse proliferation of large, atypical lymphocytes with high proliferative index and typically express the B-cell antigens CD19, CD20, and CD79a. The BCL-2 is overexpressed, whereas BCL6 is positive in more than two-thirds of cases. While in this case, proliferation of large lymphoid cells, with elongated, pleomorphic, and prominent nucleoli along with few scattered small lymphocytes were noted. Neoplastic lymphoid cells were strongly positive for CD45, CD20, CD10, BCl2 and BCl6. and negative for Pan CK, HMB 45 and C3. Ki 67 index is 65% [5-7].

Following the diagnosis of DLBCL, the oncologist advised to initiate the six cycles of R-CHOP Regimen of which four cycles were given uneventfully, but no response was noted; in fact, the size of swelling increased [8,9]. Considering the possibility of treatment failure, patient was advised Positron emission tomography (PET) scan and Repeat Biopsy as mentioned above. After the due consultation with oncologist was done with repeat PET reports and Biopsy and the regimen was modified to R-ICE to which patient responded promptly as mentioned in the case scenario.

With conventional chemotherapy, high rates of treatment failure were regarded and this was taken into the account by Nowakowski GS et al., [10]. They concluded that, there are lots of hurdles and challenges that needs to be overcome to accurately identify the molecular subsets and to govern the specific chemotherapeutic modality and targeted therapies. The pivotal strategy should be to maximise cure rates and favourable treatment outcome so as to enhance long-term survival along with curtailing the chances of toxicity. The current and future trails must be intended to improve the overall clinical outcome of patient by using biologically active compound. While additional strategy must be chalked out to address the treatment failure and include the novel and targeted agents.

Kewalramani T et al., concluded in their literature that those patient developed relapse or those had primary refractory (DLBCL) who achieve complete response (CR) prior to the autologous stem cell transplantation (ASCT) usually have better prognostic outcomes when compared to those who accomplished just partial response (PR). The study concluded that adding Rituximab to ICE combination increases the possibilities of complete response in the patients with DLBCL who are under the consideration of autologous stem cell transplant [11]. Similarly, in present case, patient was shifted from R-CHOP to R-ICE regimen, and patient achieved complete response.

Unfortunately, the patient was encountered with COVID-19 pneumonitis with acute pulmonary thromembolism and severe Acute Respiratory Distress Syndrome (ARDS) and was on Non Invasive Ventillation (NIV) support. Patient already being an immunocompromised, was more prone to secondary acquired infection and was initiated with the treatment as mentioned in [Table/Fig-5]. However, administering Tocilizumab was not considered due to its side-effect profile and its potency to flare the immunocompromise state that itself can precipitate opportunistic bacterial and fungal infection. Despite patient being immunocompromised with evidence of severe neutropenia, responded to the above treatment and was weaned off from NIV and oxygen support in next seven days and was continued with rivaroxaban. Patient was later given remaining cycles of R-ICE regimen successfully. Currently patient had complete remission. DLBCL being most common form of Non-hodgkin lymphoma. The R-CHOP regimen is a standard first line treatment whereas R-ICE is also considered in a patient who had relapse and treatment failure [11,12]. The autologous stem cell transplant is also a promising treatment; more supportive studies are needed in this regards. While target novel drugs can also be used when there is a failure of R-CHOP regimen or R-ICE regimen. It's the corollary that haematological malignancy such as lymphomas, leukaemias, myelomas cause severe myelosuppression and lymphodepletion increasing the risk for development of various virus infections such as COVID-19. Studies have shown that patients with malignancy had an estimated two-fold increased risk of contracting SARS-CoV-2 than the general population as concluded by Dai M et al., in their multicentric study [13].

CONCLUSION(S)

The DLBCL being most common form of non hodghkin lymphoma. The R-CHOP regimen is a standard first line treatment whereas R-ICE is also considered in a patient who had relapse and treatment failure. The autologous stem cell transplant is also a promising treatment; although more supportive studies are needed in this regards. While target novel drugs can also be used when there is a failure of R-CHOP regimen or R-ICE regimen. It's the corollary that haematological malignancy such as lymphomas, leukaemias, myelomas cause severe myelosuppression and lymphodepletion increasing the risk for development of various viral infections such as COVID-19 and during such circumstances, patients must be treated aggressively and with full aseptic precaution in an isolation settings.

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