

Journal of Gastroenterology and Hepatology Research

Online Submissions: <http://www.ghrnet.org/index./joghr/>
doi: 10.17554/j.issn.2224-3992.2021.10.987

Journal of GHR 2021 February 21; **10(1)**: 3456-3459
ISSN 2224-3992 (print) ISSN 2224-6509 (online)

CASE REPORT

Iatrogenic Immunodeficiency Lymphoproliferative Disorder with Hepatic Impairment Treated with Salvage Gemcitabine

Keith Brown¹, DO, MBA; Herman Suga¹, DO; Maulik Shah²; Donald McMahon², DO

1. Division of Internal Medicine, Rowan University School of Medicine at Jefferson Health System, Stratford, New Jersey, United States;

2 Division of Gastroenterology, Jefferson Health New Jersey, New Jersey, United States.

Conflict-of-interest statement: The authors declare that there is no conflict of interest regarding the publication of this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Keith Brown, Division of Internal Medicine, Rowan University School of Medicine at Jefferson Health System, Stratford, New Jersey, United States.

Email: brownke@rowan.edu

Telephone: +1-302-465-6860

Received: November 6, 2020

Revised: December 31, 2020

Accepted: January 4, 2021

Published online: February 21, 2021

ABSTRACT

Other iatrogenic immunodeficiency-associated lymphoproliferative disorders, classic Hodgkin lymphoma-type, is a subclassification of lymphoproliferative disorders typically seen in patients taking immunosuppressive medications in the setting of autoimmune diseases. Standard of care is currently Adriamycin, Bleomycin, Vinblastine, and Dacarbazine (ABVD) as it is for typical Hodgkin lymphoma, however, the side effect profile of these drugs include transaminase elevations which restrict their use in patients with underlying liver dysfunction. In patients in this clinical scenario gemcitabine has been infrequently used in the literature as salvage

therapy as well as other alternative strategies. We report a case of classic hodgkin lymphoma-type other iatrogenic immunodeficiency disorder with impaired liver function who was treated empirically with salvage therapy of gemcitabine who developed symptomatic thrombocytopenia without recovery.

Key words: Gemcitabine; Hodgkin's lymphoma; Other iatrogenic immunodeficiency-associated lymphoproliferative disorder; Chemotherapy

© 2021 The Authors. Published by ACT Publishing Group Ltd. All rights reserved.

Brown K, Suga H, Shah M; McMahon D. Iatrogenic Immunodeficiency Lymphoproliferative Disorder with Hepatic Impairment Treated with Salvage Gemcitabine. *Journal of Gastroenterology and Hepatology Research* 2021; **10(1)**: 3456-3459 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/3092>

List of abbreviations

classical Hodgkin lymphoma type (CHL-type), Adriamycin, Bleomycin, Vinblastine, and Dacarbazine (ABVD), classical Hodgkin lymphoma type, other iatrogenic immunodeficiency-associated lymphoproliferative disorders (CHL-type Oii-LPD), cyclophosphamide, etoposide, procarbazine, and prednisone (CEPP), N-acetylcysteine (NAC), Hodgkin's lymphoma (HL)

INTRODUCTION

Other iatrogenic immunodeficiency-associated lymphoproliferative disorders (Oii-LPDs) are classified as tumors of hematopoietic and lymphoid tissues occurring in those receiving immunosuppressive therapy or those with autoimmune diseases. Among this category of lymphoproliferative disorders are classical Hodgkin lymphoma type (CHL-type) which is a rare entity with very few cases reported in literature^[1]. The standard of care for Hodgkin lymphoma (HL) in the United States is currently a combination therapy of Adriamycin, Bleomycin, Vinblastine, and Dacarbazine (ABVD). However, there is a lack of data for patients who present with HL with impaired liver function and coagulopathy, as the side effect profile of traditional therapy has been reported to cause further transaminase elevations^[2,3].

Few case reports have reported utilizing bridging therapy with Gemcitabine as salvage therapy in patients with refractory HL with only mild drug related toxicities. Although several experimental alternative regimens exist, this therapy was utilized in patients who are unable to receive ABVD and have reported some success with this regimen^[1-2,4].

The best regimen of CHL-type Oii-LPD with liver impairment is yet to be established, although many regimens have been attempted with variable success^[5]. We present an unusual case of CHL-type Oii-LPD with significantly impaired liver function who was initially treated with gemcitabine, steroids, and N-acetylcysteine (NAC) as salvage therapy who developed hemodynamic instability due to symptomatic thrombocytopenia without recovery.

CASE REPORT

A 39-year-old female with a history of Systemic Lupus Erythematosus, Rheumatoid Arthritis on hydroxychloroquine, Raynaud's syndrome and alcohol abuse presented to the hospital with generalized fatigue. On arrival at the emergency department, she was found to be tachycardic and febrile with physical examination findings significant for jaundice and cervical lymphadenopathy. She received three units of packed red blood cells for worsening anemia after laboratory data revealed pancytopenia with a hemoglobin of 4.5g/dL (Hgb 12 to 16 g/dL), white blood cell (WBC) count of 2,400 B/L (3,700 to 10,500 B/L), and platelet count of 17,000 B/L (150,000 B/L to 400,000 B/L). Peripheral smear revealed pancytopenia with rare immature granulocytes, mild polychromasia and occasional nucleated RBCs with large platelets (Figure 1). Bone marrow biopsy was performed and revealed 50% of the marrow space was replaced by histiocytic infiltrate mixed with lymphocytes, plasma cells, and scattered eosinophils (Figure 2). A large area of necrosis was estimated to be 20% (Figure 3). Pax-5 stains show scattered small B cells and rare dimly positive large cells. Findings were consistent with extensive involvement by other iatrogenic immunodeficiency-associated lymphoproliferative disorders.

Lab values included elevations of her liver function test (LFT) with a total bilirubin of 5.3 mg/dL (0-1 mg/dL), direct bilirubin of 2.8 mg/dL (0-0.3 mg/dL), alkaline phosphatase of 1,270 u/L (39-117 u/L), and aspartate aminotransferase (AST) 57 u/L (normal value of < 31 u/L), alanine aminotransferase (ALT) 39 u/L (normal value of 0-31 u/L). Gamma glutamyl transpeptidase (GGT) was 116 u/L (0-30 u/L) and lactate dehydrogenase was 220 u/L (100-200 u/L). An MRI of her abdomen was performed to evaluate her transaminitis which was significant for hepatomegaly and steatosis. Due to the significant elevation of the LFTs on arrival, it was believed that the transaminitis was from a combination of patients underlying systemic lupus erythematosus, medication use of hydroxychloroquine use, and alcohol use. Due to the complexity of the patient's condition and concern of underlying liver failure she was transferred to a tertiary care center for further management.

During her hospital stay at tertiary care center the patient obtained a computerized tomography (CT) scan of her chest which revealed large bilateral axillary lymph nodes with smaller mediastinal and hilar lymph nodes. Axillary lymph node biopsy revealed atypical lymphoid infiltrate scattered large atypical cells in the background of mixed inflammatory cells (Figure 4). Large cells with single to multiple nuclei. Atypical cells were positive for CD15, CD30, and PAX-5 with overall findings consistent with classical Hodgkin lymphoma and classified as Other iatrogenic immunodeficiency associated lymphoproliferative disorders (Figure 5). The patient was discharged

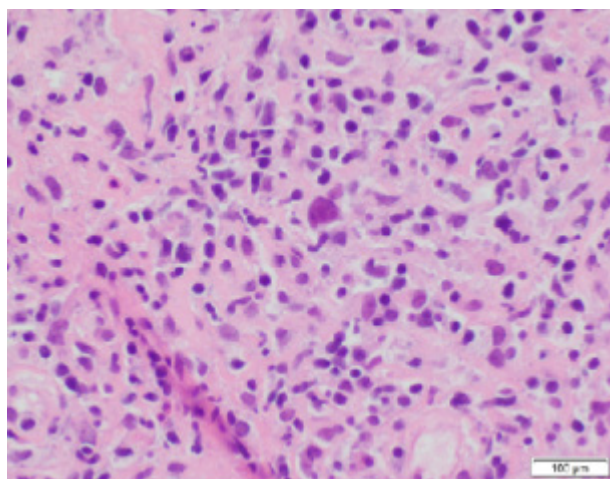


Figure 1 The large Hodgkin cells have single to multiple nuclei, prominent central nucleoli and abundant amounts of cytoplasm (400x magnification).

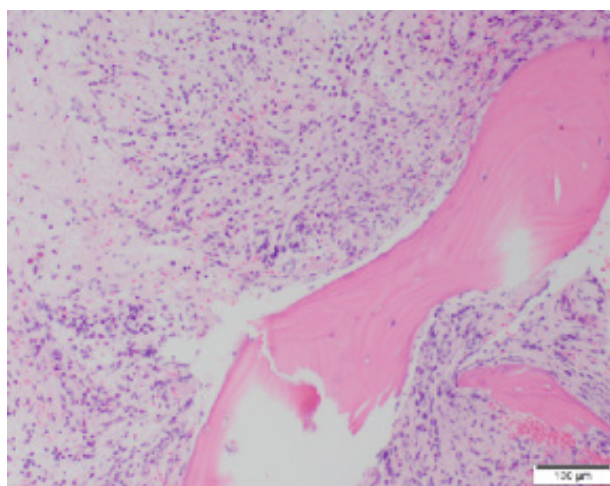


Figure 2 Bone marrow with nearly complete replacement of histiocytic infiltrates mixed with lymphocytes, plasma cells and eosinophils (100x magnification).

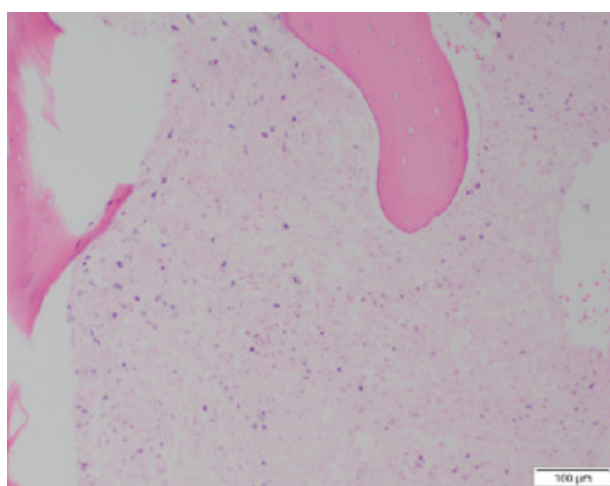


Figure 3 Bone marrow with nearly complete replacement of histiocytic infiltrates mixed with lymphocytes, plasma cells and eosinophils and large areas of necrosis (100x magnification).

home at this time and was scheduled to have a follow up appointment with hematology and oncology.

A week later, the patient was readmitted to the hospital for now concerns of worsening abdominal pain, ascites, and jaundice. She had

worsening liver function tests on arrival and was started on acetadote in the emergency department. A repeat CT of the abdomen was done showing worsening liver lesions which were highly suspicious for disseminated Hodgkin's lymphoma given findings on recent axillary lymph node biopsy and bone marrow aspiration. A liver biopsy was deferred as it would not alter the current management. The diagnosis of stage IV CHL-type Oii-LPD was made and consideration was given to start the patient on traditional ABVD therapy. Due to the hepatotoxic side effect profile of ABVD therapy, hematology decided to place the patient on gemcitabine and methylprednisolone as salvage therapy.

The patient did initially tolerate gemcitabine but then became febrile, tachycardic, and developed worsening jaundice and ascites. Her platelet count worsened to 4,000 B/L (150,000 B/L to 400,000 B/L) and she began to have recurrent epistaxis. She was upgraded to the intensive care unit due to hemodynamic instability with persistent epistaxis. Given her worsening symptoms, the family decided to place the patient on comfort care and shortly expired after this decision.

DISCUSSION

Other iatrogenic immunodeficiency-associated lymphoproliferative disorder, classic Hodgkin lymphoma-type, is a subclassification of lymphoproliferative disorders typically seen in patients taking immunosuppressive medications in the setting of autoimmune diseases^[12]. The World Health Organization (WHO) classification not only recognizes the occurrence of ILD in patients post transplant, but also in patients that are undergoing prolonged immunosuppression therapy 1. Immunosuppression has a high correlation and is a strong risk factor for Hodgkin' lymphoma incidence. Histologically, this disease subtype is characterized by scattered mononuclear and multinucleated giant cells surrounded by infiltrated non-neoplastic inflammatory cells. Immunohistochemical findings are similar to patterns seen in Classic Hodgkin lymphoma with expression of CD15, CD20, CD30, and PAX5, making the differentiation of these two disease entities difficult^[10].

Malignant infiltration of the liver with Hodgkin's disease causing acute liver failure is uncommon, but when concomitant carries a grave prognosis^[6]. There are very few case reports of patients with Hodgkin's lymphoma with acute liver failure at presentation^[15]. Due to the small percentage of patients with aggressive lymphoma and hepatic involvement the treatment options are limited^[7]. CHL is a particularly chemosensitive malignancy with high cure rates in patients treated with ABVD alone or followed by radiotherapy^[9]. This therapy has been accepted as the standard of care for decades with response rates greater than 70% even in patients with poor prognosis^[13]. Included in the standard treatment options for HL are doxorubicin and vinblastine which are metabolized in the liver complicating the treatment for patients who present with hepatic function impairment. Inferior results are typically seen with nonstandard first line chemotherapy to include dexamethasone, high dose cytarabine, and cisplatin (DHAP)^[8]. Few therapies in the literature have been shown to be effective in patients with hepatic impairment which include cyclophosphamide, etoposide, procarbazine, and prednisone (CEPP) and gemcitabine^[2,15].

Gemcitabine is a chemotherapeutic agent used widely in the treatment of cancers considered to have a good safety profile. There are very few cases of gemcitabine causing serious hepatotoxicity^[14]. Gemcitabine has been shown to potentially be effective as salvage therapy in patients with refractory/relapsed Hodgkin' lymphoma and pharmacokinetic trials have expressed that dose adjustments are not required in patients with hepatic or renal dysfunction^[2]. Due to this reason, gem-

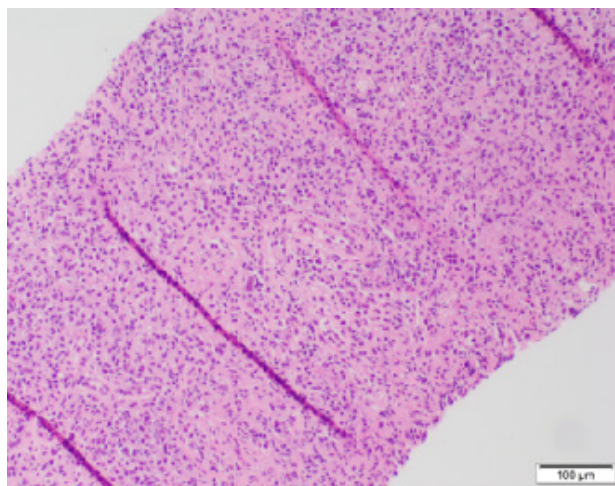


Figure 4 Right axillary lymph node fine needle cores show thin cores of lymphoid tissue with scattered large Hodgkin cells in a background of mixed inflammatory cells (100x magnification).

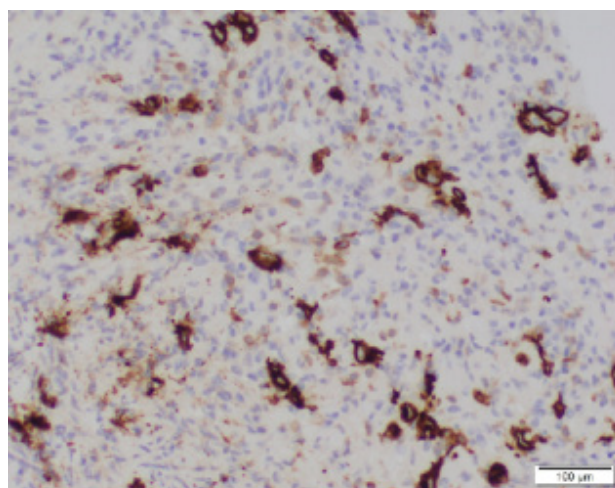


Figure 5 Immunohistochemical stain that is positive for CD30 (Fig. 5, 200x) suggesting Hodgkin lymphoma.

citabine was chosen as an attempted salvage therapy in our patient.

The diagnosis of acute liver failure alone increases mortality and has complications to include coagulopathy and encephalopathy 6. Liver biopsy was not obtained in our patient as she was significantly thrombocytopenic and the additional information obtained from a liver biopsy would not change subsequent management. In much of the literature surrounding HL with acute liver failure, biopsy of the liver is inconclusive^[6]. Our patient developed symptomatic thrombocytopenia with epistaxis requiring intensive care monitoring of hemodynamic stability complicating the treatment course of her chemotherapy. Data is lacking in the literature regarding treatment of HL and acute liver failure specifically when treatment is complicated by coagulopathy as in this patient^[2]. Ultimately this aggressive disease without adequate treatment left her inundated by the disease process and she ultimately transitioned to hospice care.

CONCLUSION

CHL-type Oii-LPD is a rare clinical entity with few cases reported in the literature. There are even fewer cases reported with associated liver failure. Due to concomitant disease, as demonstrated in this patient, treatment options are limited. It is our hope that the mortality of this patient will bring awareness for further research into treatment options for this rare patient population.

ACKNOWLEDGEMENTS

The authors declare that there is no conflict of interest regarding the publication of this paper. No financial grants or other funding was provided for this publication.

REFERENCES

- Adams B, Lazarchick J, Medina AM. Iatrogenic immunodeficiency-associated lymphoproliferative disease of Hodgkin lymphoma-like variant in a patient treated with mycophenolate mofetil for autoimmune hepatitis. *Am J Hematol.* 2010; **85**(8): 627-9. [PMID: 20658594]; [DOI: 10.1002/ajh.21753]
- Chakraborty R, Mukkamalla SKR, Gutzmore G, Chan Hon. A case of hodgkin's lymphoma with severely impaired liver function treated successfully with gemcitabine followed by ABVD. *Journal of Blood Medicine.* 2015; **6** 93-97. [PMID: 25848330]; [DOI: 10.2147/JBM.S67664]
- Eslami A, Mathur AD, Jha KK, Wang H. Acute liver failure secondary to ABVD use. *BMJ Case Rep.* 2018. [PMID: 30061135]; [DOI: 10.1136/bcr-2018-225474]
- Gupta A, Petrasek J, Sen S, Gopal P, Naina HV. Single-agent brentuximab as bridging therapy for Hodgkin lymphoma patients with hepatic impairment. *Clin Lymphoma Myeloma Leuk.* 2016; **16**(2): e11-4. [PMID: 26775723]; [DOI: 10.1016/j.clml.2015.11.015]
- Hong FS, Smith CL, Angus PE, Crowley P, Ho WK. Hodgkin lymphoma and fulminant hepatic failure. *Leuk Lymphoma.* 2010; **51**(5): 947-51. [PMID: 20367133]; [DOI: 10.3109/10428191003699571]
- Hope BC, Chau KY, Evans HM, Mouat S, Munn S, Yeong ML, Chin SE. Hodgkin disease relapse discovered at the time of liver transplant for acute liver failure. *Pediatr Transplant.* 2012; **16**(1): E10-4. [PMID: 21054714]; [DOI: 10.1111/j.1399-3046.2010.01380.x]
- Loo EY, Medeiros LJ, Aladily TN, Hoehn D, Kanagal-Shamanna R, Young KH, Lin P, Bueso-Ramos CE, Manning Jr JT, Patel K, Thomazy V, Brynes R, Goswami M, Fayad LE, Miranda RN. Classical hodgkin lymphoma arising in the setting of iatrogenic immunodeficiency: a clinicopathologic study of 10 cases. *Am J Surg Pathol.* 2013; **37**(8): 1290-7. [PMID: 23774171]; [DOI: 10.1097/PAS.0b013e31828e6564]
- McCarthy J, Gopal AK. Successful use of full-dose dexamethasone, high-dose cytarabine, and cisplatin as part of initial therapy in non-hodgkin and hodgkin lymphoma with severe hepatic dysfunction. *Clin Lymphoma Myeloma.* 2009; **9**(2): 167-70. [PMID: 19406729]; [DOI: 10.3816/CLM.2009.n.039]
- Mesguich C, Cazeau AL, Bouabdallah K, Soubeyran P, Guyot M, Milpied N, Bordenave L, Hindié E. Hodgkin lymphoma: a negative interim-PET cannot circumvent the need for end-of-treatment-PET evaluation. *Br J Haematol.* 2016; **175**(4): 652-660. [PMID: 27539369]; [DOI: 10.1111/bjh.14292]
- Momose S, Tamaru J. Iatrogenic immunodeficiency-associated lymphoproliferative disorders of B-cell type that develop in patients receiving immunosuppressive drugs other than in the post-transplant setting. *J Clin Exp Hematop.* 2019; **59**(2): 48-55. [PMID: 31257345]; [DOI: 10.3960/jslrt.19014]
- Rafiq M, Hayward A, Warren-Gash C, Denaxas S, Gonzalez-Izquierdo A, Lyrtzopoulos G, Thomas S. Allergic disease, corticosteroid use, and risk of Hodgkin lymphoma: A United Kingdom nationwide case-control study. *J Allergy Clin Immunol.* 2020; **145**(3): 868-876. [PMID: 31730878]; [DOI: 10.1016/j.jaci.2019.10.033]
- Saburi M, Ogata M, Yoshida N, Nashimoto Y. Other iatrogenic immunodeficiency-associated lymphoproliferative disorder, hodgkin type, following epstein-barr viral hepatitis in a patient with rheumatoid arthritis. *Intern Med.* 2018; **57**(8): 1145-1149. [PMID: 29279493]; [DOI: 10.2169/internalmedicine.9599-17]
- Shaikh H, Shaikh S, Kamran A, Mewawalla P. Cholestatic jaundice: a unique presentation leading to the diagnosis of HLH with hodgkin lymphoma, HIV, and EBV. *BMJ Case Rep.* 2018. [PMID: 29754142]; [DOI: 10.1136/bcr-2018-224424]
- Stellman A, Loke MM, Mann S. Acute liver failure secondary to gemcitabine. *BMJ Case Rep.* 2010. [PMID: 22736319]; [DOI: 10.1136/bcr.12.2008.1371]
- Thakar K, Novero, Das Arundhati, Lisinschi A, Mehta B, Ahmed T, Liu D. CEPP regimen (cyclophosphamide, etoposide, procarbazine and prednisone) as initial treatment for Hodgkin lymphoma patients presenting with severe abnormal liver function. *Biomarker Research.* 2014; **2**: 12. [PMID: 24991411]; [DOI: 10.1186/2050-7771-2-12]