Paraneoplastic diseases associated with non-Hodgkin's lymphoma – Case series

Abhraneel Guha[1], Kundan Chaurasia[2], Bhaswati Dasgupta Nath[3], Raja Basu[3], Avijit Das[3], Digbijoy Choudhury[4], Mandeep Joshi[1], Ajoy Krishna Sarkar[5]

From [1]Postgraduate, [2]Head of the Unit, [3]Consultant, [4]Senior Registrar, [5]Director Critical Care Medicine and Head of Unit Internal Medicine, Department of Internal Medicine, Peerless Hospital and B.K. Roy Research Centre, Kolkata, West Bengal, India

Correspondence to: Ajoy Krishna Sarkar, Department of Internal Medicine, Peerless Hospital and B.K. Roy Research Centre, Kolkata, West Bengal, India. E-mail: ajoysarkar29@gmail.com

Received - 09 June 2020 Initial Review - 02 July 2020 Accepted - 22 August 2020

ABSTRACT

Non-Hodgkin's lymphoma (NHL) is malignancies of white blood cells called lymphocytes. Although fever and weight loss are the main symptoms associated, NHL is known for its unusual presentation. Variants of NHL include diffuse large B cell, Mantle cell, Burkitt's Lymphoma, Precursor B cell type, and among many. At times, paraneoplastic diseases often mask the underlying lymphoma and hence delaying the diagnosis. Through this case series, we discuss the association of NHL with paraneoplastic diseases. NHL was associated with dorsal myelitis in the first case, metastatic spread in abdomen in the second case and with Steven Johnson syndrome in the third case.

Key words: *Diffuse large B cell lymphoma, Ki-67, Non-Hodgkin's lymphomas, Paraneoplastic disease*

Lymphoma may present in various ways and can be associated with paraneoplastic neurological symptoms. Paraneoplastic neurological disease (PND) is a group of diseases that occur in patients with cancer and not due to the presence of metastasis or direct infiltration of the tumor into the nervous system [1]. They are associated with lung carcinoma, lymphoma, and gynecological tumors. They affect the prognosis of malignancy; therefore, its diagnosis at earlier stage is crucial. In this case series, we discuss three clinical scenarios of Non-Hodgkin lymphoma (NHL) associated with paraneoplastic diseases (NHL).

CASE REPORT 1

A 28-year-old female patient presented with pain in left side of abdomen since 20 days which was radiating to back. She also complained about mild shortness of breath. Previously, she had consulted a different hospital before 2 months and investigations were carried out. With the investigative reports of diagnostic and therapeutic pleural fluid tapping, abdominal ultrasonography (USG), contrast-enhanced computed tomography (CECT), thorax and abdomen and laboratory investigations, we deduced a differential diagnosis of malignancy, Koch's and infective pathology. Nevertheless, all baseline routine investigations were carried out in our hospital, which were within normal limits. Abdominal USG revealed a nodular region in paraaortic region, enlarged lymph node, and a focal area of hypoechoic region in anterior cortex of the left kidney. CECT whole abdomen revealed ill-defined left paraaortic region, upper pole of left kidney suggestive of mitotic, Koch's or infective origin. Since Koch or infective etiology could coexist, exploratory laparotomy was done under general anesthesia and sample was sent for gene expert. However, since the report was negative, tuberculosis was ruled out. Fine-needle aspiration cytology (FNAC) of the adrenal cortex showed mononuclear cells with high nuclear to cytoplasmic ratio and anisochromasia (Fig. 1). Immunohistochemistry reports of the sample confirmed diffuse large B cell lymphoma.

Patient was empirically started on IV antibiotics piperacillin/tazobactam. However, after few days, patient developed symptoms of inadequate voiding and weakness of both lower limbs. USG was suggestive of retention of urine. Neurological examination revealed decreased left lower limb power and normal right lower limb power. On neurological consultation, magnetic resonance imaging (MRI) LS spine (Fig. 2) was done which was suggestive of dorsal myelitis. Since, paraneoplastic involvement of spine was suspected; patient was started on IV methylprednisolone with good response rate and later shifted to oral methylprednisolone when she regained left lower limb power. Kidney function also returned to normal and urine output improved. Subsequently, chemotherapy was initiated.

CASE REPORT 2

A 68-year-old female patient with known history of tuberculosis and space occupying lesion in the left anterior chest wall since 4 years, reported to us with low to moderate grade fever associated with profuse sweating since 2 weeks. On admission, all routine investigations were done which revealed low hemoglobin, leukopenia, normal platelet count, raised total

bilirubin, hypoalbuminemia, raised SGPT and SGOT, alkaline phosphatase, and CRP. Despite IV antibiotics, there was no improvement. Patient's blood culture (aerobic and fungal) was done as fever spikes persisted which did not yield any growth. Patient suspected to have leptospirosis, kala azar, lymphoma, and pheochromocytoma. Echocardiography revealed normal left ventricular ejection fraction with apical hypokinesia. Ultrasonography of whole abdomen revealed moderate hepatosplenomegaly with bilateral suprarenal nodules, larger on the left side. No ascites and lymphadenopathy were seen. Abdominal CECT revealed left adrenal mass measuring of about 3.7 cm × 3 cm diameter, along with the right suprarenal mass (Fig. 3). FNAC was suggestive of lymphoproliferative disorder. Patient underwent surgery and biopsy of the tissue confirmed it to be diffuse large B cell lymphoma, a variant of NHL.

CASE REPORT 3

A 52-year-old male patient was admitted with drug induced rash with mucosal involvement since a month. Since patient was suspected to have Steven Johnson syndrome, precautions were taken. Despite management with antibiotics, fever and rash persisted and he developed bowel incontinence. USG (Fig. 4) revealed splenomegaly with multiple splenic nodular deposits, retroperitoneal lymphadenopathy, mild ascites, bilateral pleural effusion, right lump, and cervical lymphadenopathy. Lymph node biopsy was negative for tuberculosis. However, analysis of ascitic fluid revealed atypical lymphoid cells with mucinous mononuclear cells and smudge lymphadenopathy, and occasional mesothelial cells suggestive of possible NHL. Microscopic features of skin biopsy (Fig. 5) were suggestive of mycosis fungoides, a cutaneous involvement of NHL. Immunohistochemistry was positive for CD 30. In addition, biopsy of cervical lymph node revealed features strongly positive for CD 30 lineage suggesting NHL. Although initially patient's condition improved with appropriate treatment, due to multiorgan involvement the condition deteriorated and he succumbed to death.

DISCUSSION

NHL represent a heterogeneous group of malignancies that arise from the lymphoid system whose etiology remains elusive [2]. Tumor suppressive miRNAs are found to be dysregulated

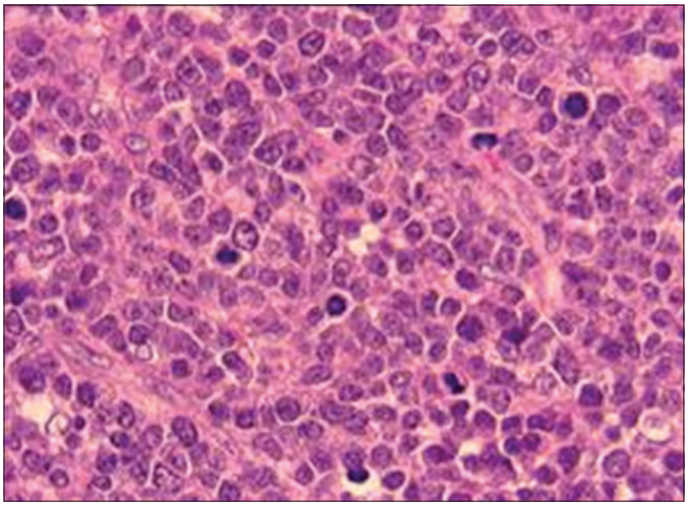

Figure 1: Microscopic picture showing diffuse large B-Cell lymphoma

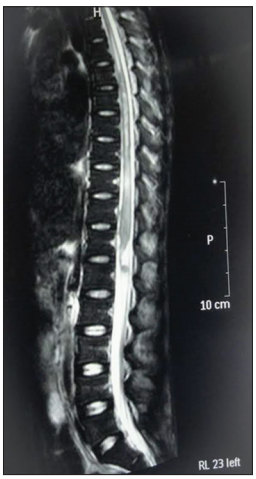

Figure 2: Magnetic resonance imaging spine showing dorsal myelitis

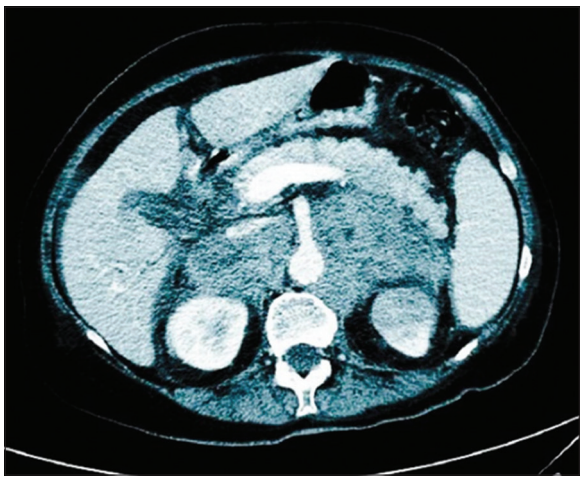

Figure 3: CT abdomen showing bilateral adrenal involvement of space occupying lesion

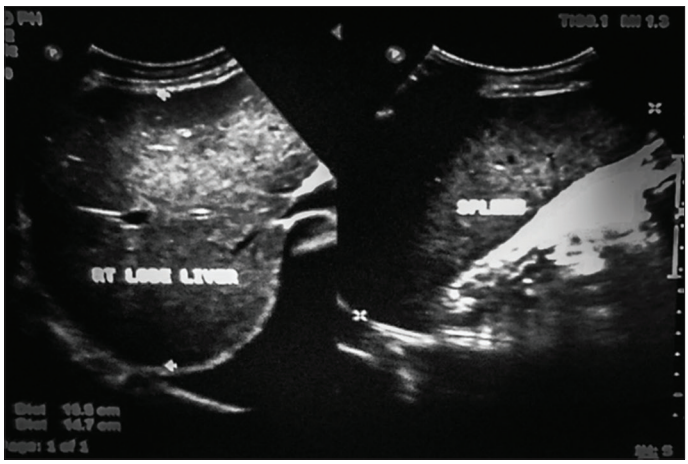

Figure 4: Ultrasonography showing splenomegaly and multifocal splenic deposits

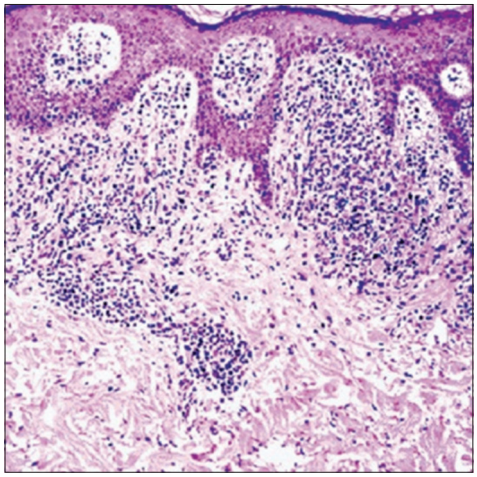

Figure 5: Microscopic appearance of mycosis fungoides

in lymphomas and they influence the disease progression, transformation, and drug resistance in lymphomas. Furthermore, there is repression of NFKB1 which affects the disease transformation [3]. Ki-67 is a nuclear protein involved in cell proliferation regulation, and its expression has been widely used as an index to evaluate the proliferative activity of lymphoma and is identified in patient with fatal NHL [4]. Introduction of gene expression profiling helps identify the novel oncogenic pathways involved in the process of malignant transformation and novel molecular lymphoma subtypes that are histologically indistinguishable [5]. Furthermore, Ann Arbor staging for NHL helps staging and depicts the prognosis. While, high risk patients may benefit from new experimental approaches, on the other hand, low risk patients respond well to standard therapy may experience drug reactions for new experimental regiments [6].

Paraneoplastic disease (PND) is a complication of malignancy occurring in less than 0.01% of patients [1]. It affects the central and peripheral nervous systems, muscles, and neuromuscular junctions. Symptoms include encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, opsoclonus-myoclonus, subacute sensory neuronopathy, autonomic neuropathies, myasthenia gravis, Lambert-Eaton myasthenic syndrome, or dermatomyositis [7]. Immunogenic paraneoplastic syndrome can appear as myelopathy with underlying pathological findings such as inflammation, demyelination, and necrosis [8].

Paraneoplastic involvement of spinal cord causes neurological symptoms of myelopathy. The tumor cells may directly invade the spinal cord proper or can undergo spinal tumor cell infiltration of contributory vessels derived from tumor cells [9]. MRI may be normal or show spinal cord enlargement without any contrast medium enhancement. The absence of epidural mass or discrete intramedullary enhancement rules out metastatic myelopathy which is more common. Treatment is usually unsuccessful; however, there are some reports which show response to steroids or underlying malignancy therapy [10]. In our first case, the MRI spinal cord findings were suggestive of dorsal myelitis and patient responded well to steroid therapy.

The majority of gastrointestinal lymphomas originate in stomach, followed by small intestine involving retroperitoneal and mesenteric lymph nodes [11]. According to Nakamura *et al*., treatment approach for gastrointestinal lymphoma includes, surgical procedures followed by radiotherapy, chemotherapy, and immunotherapy [12]. However, the importance of surgery before chemotherapy is elusive. It has been known that overall survival rate of low and high grade lymphomas is similar; however, the event free survival is worse in patients with simultaneous low-grade component than in high-grade lymphomas along with other factors, the overall survival of patients depends on the grading system and treatment strategies undertaken [12]. Our second case underwent surgery for the lymphoma in abdomen, followed by chemotherapy and survived.

Patients treated with immunotherapy for inflammatory bowel disease have an increased risk of lymphoma as a result of the medications, the severity of the underlying disease, or a combination of the two [13]. NHL is an opportunistic disease found in 2.9% patients diagnosed with AIDS [14]. Association between Steven Johnson syndrome and NHL has also been found [15]. In the third patient, due to the presence of rashes he was treated for Steven Johnson syndrome. Since the patient was nonresponsive to the treatment further investigations were carried out which showed presence of NHL along with altered bowel movement. He was treated according to the guidelines of American Cancer Society, however, due to severity of disease he succumbed to multiorgan failure.

CONCLUSION

NHL can be a life-threatening disease, identification with B-67 in immunohistochemical techniques helps in early diagnosis of fatal NHL. Blood parameters must be monitored to identify multiorgan involvement. Although PND is not a common complication of NHL, yet its identification is crucial. In our cases, management of these paraneoplastic diseases before the treating NHL improved the survival rates of the patients. However, further studies needs to be carried out to confirm the time of the management of paraneoplastic diseases.

REFERENCES

1. Blaes F. Immunotherapeutic approaches to paraneoplastic neurological disorders. Expert Opin Investig Drugs 2000;9:727-33.
2. Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. CA Cancer J Clin 2001;51:15-36.
3. Joshi T. The Role of miRNA Regulation in Cancer Progression and Drug Resistance. Denmark: Technical University of Denmark; 2012. p. 106.
4. He X, Chen Z, Fu T, Jin X, Yu T, Liang Y, *et al*. Ki-67 is a valuable prognostic predictor of lymphoma but its utility varies in lymphoma subtypes: Evidence from a systematic meta-analysis. BMC Cancer 2014;14:153.
5. Ballester B, Ramuz O, Gisselbrecht C, Doucet G, Loï L, Loriod B, *et al*. Gene expression profiling identifies molecular subgroups among nodal peripheral T-cell lymphomas. Oncogene 2006;25:1560-70.
6. Popescu RA, Wotherspoon AC, Cunningham D, Norman A, Prendiville J, Hill ME. Surgery plus chemotherapy or chemotherapy alone for primary intermediate- and high-grade gastric non-Hodgkin's lymphoma: The Royal Marsden Hospital experience. Eur J Cancer 1999;35:928-34.
7. Jaffe ES. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. France: International Agency for Research on Cancer; 2001.

8. Sadahira Y, Wada H, Nakamura E, Terayama K, Sugihara T, Yamada O, *et al*. Nasal NK/T cell lymphoma presenting as transverse myelopathy. Virchows Arch 2000;436:393-7.
9. Mathur S, Law AJ, Hung N. Late intramedullary spinal cord metastasis in a patient with lymphoblastic lymphoma: Case report. J Clin Neurosci 2000;7:264-8.
10. Angelopoulou MK, Vassilakopoulos TP, Konstantinou E, Boutsikas G, Asimakopoulos JV, Triantafyllou EF, *et al*. Central nervous system involvement in primary bone marrow or splenic marginal zone lymphoma: Report of two cases and review of the literature. Hematol Oncol 2019;37:219-22.
11. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Eng J Med 1993;329:987-94.
12. Nakamura S, Matsumoto T. Gastrointestinal lymphoma: Recent advances in diagnosis and treatment. Digestion 2013;87:182-8.
13. Fisher SG, Fisher RI. The epidemiology of non-Hodgkin's lymphoma. Oncogene 2004;23:6524-34.
14. Koch P, Del Valle F, Berdel WE, Willich NA, Reers B, Hiddemann W, *et al*. Primary gastrointestinal non-Hodgkin's lymphoma: II. Combined surgical and conservative or conservative management only in localized gastric lymphoma--results of the prospective German multicenter study GIT NHL 01/92. J Clin Oncol 2001;19:3874-83.
15. Cuthbert RJ, Craig JI, Ludlam CA. Stevens-Johnson syndrome associated with methotrexate treatment for non-Hodgkin's lymphoma. Ulster Med J 1993;62:95-7.

Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Guha A, Chaurasia K, Nath BD, Basu R, Das A, Choudhury D, *et al*. Paraneoplastic diseases associated with non-Hodgkin's lymphoma – Case series. East J Med Sci. 2020;5(3):66-69.

Doi: 10.32677/EJMS.2020.v05.i03.005