



A RARE CASE OF PULMONARY LANGERHANS CELL HISTIOCYTOSIS OCCURRING FOLLOWING HODGKIN'S LYMPHOMA

Vipal H. Parmar, Prashant M.Parikh, Bhavna A. Mehta, Sandip C. shah, Rutvik J. Raval, Mandava V. Rao[★]

Department of Histopathology, Neuberg Supratech Referral Laboratory, Opp. Krupa Petrol Pump, Nr Parimal Garden, Ahmedabad 380006, India.

Article Info

*Corresponding Author:

Mandava V Rao

Email: manvrao@gmail.com

Abstract

Adult pulmonary Langerhans Cell histiocytosis (LCH) is a rare disorder of unknown aetiology. The occurrence of Pulmonary Langerhans Cell Histiocytosis (LCH) in a patient with Hodgkin's disease is an indication of a probable relationship between them. The two conditions have similarities both clinically and histopathologically. Several cases of Langerhans' cell histiocytosis associated with Hodgkin's disease (before, concurrent or after lymphoma) have been reported in the literature. Occurrence of pulmonary LCH after Hodgkin's lymphoma is rare. However, we describe a rare case of Pulmonary Langerhans Cell Histiocytosis occurring after partial treatment for nodular sclerosis Hodgkin's lymphoma, diagnosed while follow up investigations of Hodgkin's disease and patient presented as pulmonary LCH with residual/recurrent Hodgkin's disease.

Key words: Langerhans Cell Histiocytosis, Hodgkin's lymphoma.

Introduction:

Langerhans cells are antigen presenting cells (APCs), residing in the skin, the mucosa of certain organs and lymphoid tissue. Abnormal proliferation of such cells covers a large spectrum of rare disorders called Histiocytosis X or collectively Langerhans Cell Histiocytosis (LCH). It is further associated with Hodgkin's disease before, during and after treatment of lymphoma [1, 2]. Several ways have depicted

the relationship between LCH and Hodgkin's lymphoma - therapy of Hodgkin's disease, immune response to Hodgkin's disease and etiological agent to both conditions [1]. We report here a case with Pulmonary LCH following Hodgkin's lymphoma treatment, in India which is rare.

Key-Messages:

A 64-year female patient presented with right upper lobe lung mass. The clinical details revealed that patient was diagnosed nodular sclerosis Hodgkin's lymphoma in cervical lymph node biopsy in 2015. She was partially treated with chemo radiation for Hodgkin's disease and after 2 years in 2017 during follow up investigations she presented with right upper lobe lung mass and mediastinal lymph nodes enlargement on radiology. Tru cut biopsy from right lung mass as well as mediastinal lymph node biopsy were performed with clinical suspicion of recurrent or residual Hodgkin's disease.

Histopathological examination of lung biopsy revealed marked interstitial infiltrate composed of eosinophils, neutrophils, lymphoplasmacytic cells and many histiocytes having cleaved nuclei, prominent vascular channels and foci of fibrosis. Typical R-S cells were not found. Immunohistochemistry results showed these histiocytes were positive for CD1a and S100 and biopsy was negative for R-S cells [Figure 1].

Histopathological examination of mediastinal lymph node revealed disarray of nodal architecture with prominent areas of sclerosis, few plasma cells and few large cells resembling R-S cells. IHC profile from mediastinal lymph node was negative for CD1a and S100 and showed R-S cells which were positive for CD30, CD15 and PAX5 and negative for CD45 [Figure 2].

Figure 1. Tru cut biopsy from lung; (A) H and E, $\times 100$ - marked interstitial infiltrate composed of eosinophils, neutrophils, lymphoplasmacytic cells and many histiocytes **(B)** H and E, $\times 400$ Eosinophil rich mixed inflammatory infiltrate with many histiocytes having cleaved nuclei-see black arrow **(C)** **CD1A immunostain**, $\times 400$ Positive in these histiocytes **(D)** **S100 immunostain**, $\times 400$ Positive in these histiocytes **(E)** **CD68 immunostain**, $\times 400$ Positive in histiocytes **(F)** **CD30 immunostain**, $\times 100$ Negative for R-S cells.

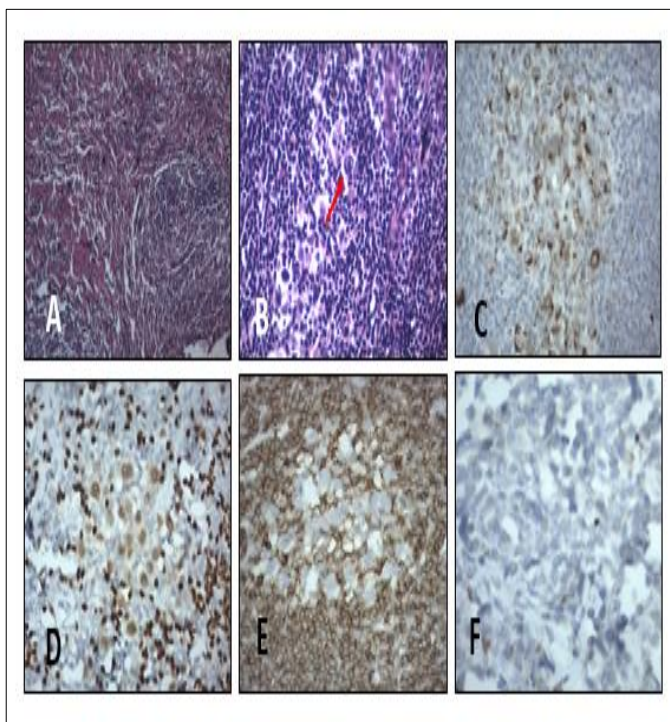
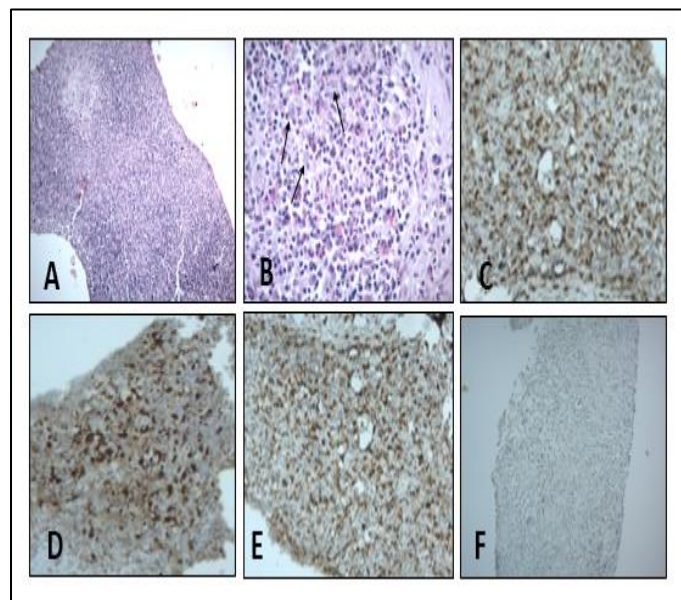


Figure 2: Mediastinal lymph node biopsy (A) H and E, $\times 100$ disarray of nodal architecture with formation of nodules separated by prominent areas of sclerosis **(B)** H and E, $\times 400$ R-S cells (red arrow) **(C)** **CD 30 immunostain**, $\times 400$ Positive in R-S cells **(D)** **PAX5 immunostain**, $\times 400$ Positive in R-S cells **(E)** **CD45 immunostain**, $\times 400$ Negative in R-S cells **(F)** **CD1A immunostain**, $\times 400$ Negative.



Previous biopsy and IHC reports done from cervical lymph node during initial diagnosis of Hodgkin's disease were also verified.

Overall histopathology and IHC was concluded as residual or recurrent Hodgkin's disease in mediastinal lymph node with concurrent pulmonary langerhans cell histiocytosis in right upper lobe lung mass

Discussion:

Langerhans cells are non-pigmented, bone marrow-derived dendritic cells. As such, they function as antigen-presenting cells that are vital to the epidermal component of the immune system [2]. These cells share certain properties with monocytes and macrophages, but differ from other histiocytes in that they are CD1a-positive, with pale clefted nuclei, abundant pale eosinophilic cytoplasm, and Birbeck granules [3]. Their most striking histological feature, which is absent in HL, is the presence of abundant eosinophils. In contrast, HL has histologically distinct Reed-Sternberg cells that are not present in LCH. Depending on the clinical course and classification, LCH can be treated with many different therapeutic strategies, including benign neglect and observation, local treatment, immunomodulation, irradiation, chemotherapy and allogenic stem cell transplantation [2]. Occurrence of LCH after Hodgkin's lymphoma is rare and is less than 0.3% of cases [5]. In a series of 39 cases of LCH and malignant neoplasia, Egeler *et al* [4] found an association between the two conditions and suggested that when LCH is associated with lymphoma, wherein the timing and unifocal involvement suggest a reactive process as result of a specific dendritic cell reaction. Another series of five cases of concurrent LCH and HD also supported that malignant lymphoma may directly or indirectly stimulate the proliferation of LCH [5]. However, in a case of sequential discordant malignant lymphoma Adu-Poku *et al* suggested a degree of interdependence between the development of LCH and malignant lymphoma [3]. Similar case of pulmonary Langerhans' cell histiocytosis after chemotherapy of nodular sclerosis Hodgkin's disease was described by Shin *et al* which speculated a common etiological agent that induces both diseases and Langerhans' cell proliferation caused by tissue damage secondary to radiotherapy and chemotherapy

for Hodgkin's disease [1]. It was observed that proliferation of Langerhans cells in association with CHL does not appear to portend a worse prognosis, and there have been anecdotal reports of favourable outcomes without additional therapy beyond the CHL-specific regimen [6]. In patients with HL appropriate genetic predisposition and exposure to tobacco probably plays a role in triggering the overt development of LCH in the lungs. Cessation of smoking and a careful follow-up examination without treatment seems suitable as an initial work-up in these patients [7] [Table 1].

Presence of Langerhans cells could correspond to two distinct pathologies: either a neoplastic monoclonal disease, or a polyclonal process in reaction to neoplasm. Another hypothesis for the association of Langerhans cells with HL is that inflammatory cells constituting the background of HL could secrete cytokines stimulating the differentiation of myeloid dendritic cells into Langerhans cells [8]. The possibility of shared risk factors for both diseases, leading to favourable conditions for tumour growth or even of a common etiological factor, should also be explored. Potential risk factors are genetic, environmental or related to defective immune systems. If these views are accepted, it remains to be investigated the reason why all patients with HL do not develop a reactive histiocytic proliferation, and why LCH sometimes occurs before the neoplasia is diagnosed, and other occasions in absence of any other malignant neoplasm. Pina-Oviedo *et al* [9] assessed for BRAF and MAP2K1 mutations in seven cases of Langerhans cell histiocytosis detected incidentally in biopsies involved by lymphoma. All cases were negative for BRAF V600E and MAP2K1 mutations. Their study concluded that lymphoma-associated Langerhans cell histiocytosis is a clinically benign process, not associated with BRAF V600E or MAP2K1 mutations. Hence, the designation Langerhans

Table 1- Summery of literature reviewed.

Sr. No	Study / Case reports	No of cases, age group and gender	Association of LCH with HL		
			HL preceding LCH	Concurrent Diagnosis of HL and LCH	LCH preceding HL
1	Egeler et al [4]	25 16-40 year 15 M,7 F, 3 NA	09 (various presentation)	15 (various presentation)	01
2	Myung et al [1]	01 20/F	01 Pulmonary LCH	-	-
3	Burns et al [5]	05 18 to 33year 3 M,2 F	-	05 (various presentation)	-
4	Adu-Poku et al [3]	01 56/F	01 Inguinal LN Hlf/b LCH in breast and nasopharyngeal mass	-	-
5	Ibarrola et al [11]	01 37/M	-	01 Right cervical LN	-
6	Soo Park et al [2]	01 22/M	-	-	01 thoracic and lumber spine LCH f/b right cervical HL
7	Seung et al [12]	01 48 /M	-	01 Thoracic spine	-
8	Safaei et al [13]	01 23/M	-	-	01 Right iliac bone LCH f/b nodal HD MC
9	Nahid et al [14]	01 10 /M	01 Cervical and submandibular mixed cellularity HL f/b scalp LCH	-	-
10	Claire et al [8]	01 10/F	-	01 (nodal LCH)	-
11	Feuillet et al [7]	02 36 /M, 29 /F	01 (pulmonary LCH)	01(pulmonary LCH)	-
12	Xin et al [15]	01 31 / M	-	-	01 Ileac bone and mediastinal mass LCH f/b Nodal NSCHL
13	Wesley et al [6]	01 28/M	-	01 Ribs, lung, neck LN- LCH and NSCHL	-
14	Pina-Oviedo et al [9]	05 28-84 year 3 M, 2 F	05 HL lymph nodes and chest wall f/b LCH	-	-
15	Shanxiang et al [10]	01 13/M	-	01 LN CHL	-
16	Present case	01 64/F	01 nodal NSCHL f/b pulmonary LCH	-	-

HL-Hodgkin's lymphoma,LCH- Langerhans' cell histiocytosis, NSCHL- Nodular sclerosis Hodgkin's lymphoma, M-male, F- female, NA-not available, f/b- followed by

cell hyperplasia may be more appropriate. However, BRAF V600E mutation was demonstrated in a typical case of LCH associated with lymphoma, supporting that at least some of the LCHs associated with lymphoma are true neoplasm [10-15]. Thus, it remains controversial if LCH associated with lymphoma represents a true neoplasm and underlying mechanism along with probable genetic mutation should be further explored [Table 1].

Conclusion:

In conclusion, we describe a case in which LCH developed after partial treatment of HD, presented as pulmonary LCH with residual /recurrent Hodgkin's lymphoma in mediastinal node and it is a rare case in India so far reported. Our case is supporting the hypothesis of therapy and immune response to Hodgkin's disease and common etiological agent to both conditions for such association. Review of literature show association of these two disease conditions are more than incidental and the significance of this association and underlying mechanism along with probable genetic mutation should be further explored in regards to the clinical aspects and disease management.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms with all necessary information.

Financial support and sponsorship: Nil.

Conflict of interest: The authors have no conflict of interest.

References:

- [1.] Myung S. Shin, Scott E. Buchalter, Kang-Jey Ho, Birmingham, Alabama *et al.* Langerhans' cell histiocytosis associated with Hodgkin's disease - a case report. *J Natl Med Assoc.* 1994; 86: 65-69.
- [2.] Soo Park IK, In Keun Park, Eun Kyoung Kim, Shin Kim, Sang Ryong Jeon, Joo Ryung Huh *et al.* Langerhans Cell Histiocytosis Followed by Hodgkin's Lymphoma. *Korean J Intern Med* 2012; 27:459-462.
- [3.] Adu-Poku K, Thomas DW, Khan MK, Holgate CS, Smith ME. Langerhans cell histiocytosis in sequential discordant lymphoma. *J Clin Pathol* 2005; 58:104-106.
- [4.] Egeler RM, Neglia JP, Puccetti DM, Brennan CA, Nesbit ME. Association of Langerhans cell histiocytosis with malignant neoplasms. *Cancer* 1993; 71:865-873.
- [5.] Burns BF, Colby TV, Dorfman RF. Langerhans' cell granulomatosis (histiocytosis X) associated with malignant lymphomas. *Am J Surg Pathol* 1983; 7:529-533.
- [6.] Wesley O. Greaves, Carlos Bueso-Ramos, Luis Fayad. Classical Hodgkin's Lymphoma Associated with Langerhans Cell Histiocytosis-Multiagent Chemotherapy Resulted in Histologic Resolution of Both the Classical Hodgkin's Lymphoma and Langerhans Cell Proliferation Components. *Journal of clinical oncology* 2011; 29: e76-e78.
- [7.] Feuillet S., L. Louis, A. Bergeron, A. Berezne, Dubreuil, M. Polivka *et al.* Pulmonary Langerhans cell histiocytosis associated with Hodgkin's lymphoma. *Eur Respir Rev ERSJ* 2010; 19: 115, 86-88.
- [8.] Claire Geurten, Albert Thiry, Paul Jamblin, Martine Demarche, Claire Hoyoux. Concomitant nodal involvement by Langerhans cell histiocytosis and Hodgkin's lymphoma. *Pediatrics international* 2015; 1214-1217. doi: 10.1111/ped.12724.
- [9.] Pina-Oviedo S, Medeiros LJ, Li S, Khoury JD, Patel KP, Alayed *et al.* Langerhans cell histiocytosis associated with lymphoma: an incidental finding that is not associated with BRAF or MAP2K1 mutations. *Mod Pathol* 2017; 30:734-744.
- [10.] Shanxiang Zhang, Julia Steinhilber, Falko Fend, Langerhans cell histiocytosis associated with classical Hodgkin lymphoma contains BRAF V600E mutation, *Annals of Hematology* 2018. <https://doi.org/10.1007/s00277-018-3425-3>.
- [11.] Ibarrola de Andres C, Toscano R, Lahuerta JJ, Martinez-Gonzalez MA. Simultaneous occurrence of Hodgkin's disease, nodal Langerhans' cell histiocytosis and multiple

- myeloma IgA (kappa). *Virchows Arch* 1999; 434:259-262.
- [12.] Seung-Jae Hyun, Seung-Chul Rhim, Jooryung Huh. Simultaneous Occurrence of Hodgkin's Lymphoma and Langerhans Cell Histiocytosis of the Spine: A Rare Combination. *Korean Neurosurg Soc* 2010; 47:302-305.
- [13.] Safaei A, Bagheri M, Shahryari J, Noori S, Esmailzade E. Langerhans Cell Histiocytosis Followed by Hodgkin Lymphoma: A Case Report, *Iran J Med Sci* 2015; 40: 282-286.
- [14.] Nahid Reisi Dehkordi, Parvin Rajabi, Azar Naimi, Mitra Heidarpour. Langerhans cell histiocytosis following Hodgkin lymphoma- a case report from Iran. *JRMS* 2010; 15: 58-61.
- [15.] Xin Li, Qi Deng, Yu-Ming Li. A case of Langerhans cell histiocytosis following Hodgkin's disease. *Molecular and clinical oncology* 2016;5: 27-30.