Case title: A 13-year-old boy presented with generalized lymphadenopathy

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Clinical history: A 13-year-old boy presented a painless left cervical adenopathy, increased fatigue, loss of appetite, occasional mild night sweats and a 30-pound weight loss for five months. CT imaging study of the chest, abdomen and pelvis showed multiple enlarged lymph nodes with largest measuring 4.5 cm in the left neck, mediastinum, left hilum, epigastrium, splenic hilum, and peripancreatic areas. Multiple splenic lesions (largest 3.1 cm) were also identified. Liver was unremarkable. An excisional biopsy of left supraclavicular lymph node was performed.

Gross examination: The excised specimen consisted of two portions of red-tan soft tissue, measuring 2.5 cm and 0.8 cm at greatest dimension.

Microscopic examination and immunohistochemistry: See attached images

The reveal: An excisional biopsy of enlarged left supraclavicular lymph node showed extensive nodal architectural effacement by a nodular proliferation containing scattered large atypical mononucleated, binucleated and multinucleated cells with prominent eosinophilic nucleoli in the background of eosinophils, small lymphocytes, and plasma cells. The large atypical cells were positive for PAX-5 (weak), CD30 and CD15 (partial), and negative for CD3, CD20, CD45RB, and ALK-1 by immunohistochemical stains (Fig.1A to C). In addition, there were multiple distinct sheets of large cells with nuclear grooves and abundant eosinophilic cytoplasm, which were positive for CD43, CD1a, S-100, and langerin, confirming them to be Langerhans cells (Fig.1D to F). Repeated next-generation sequencing of microdissected Langerhans cells identified the BRAF V600E mutation with an allele frequency of 2% to 4%, whereas no MAP2K1 hotspot mutations were identified.

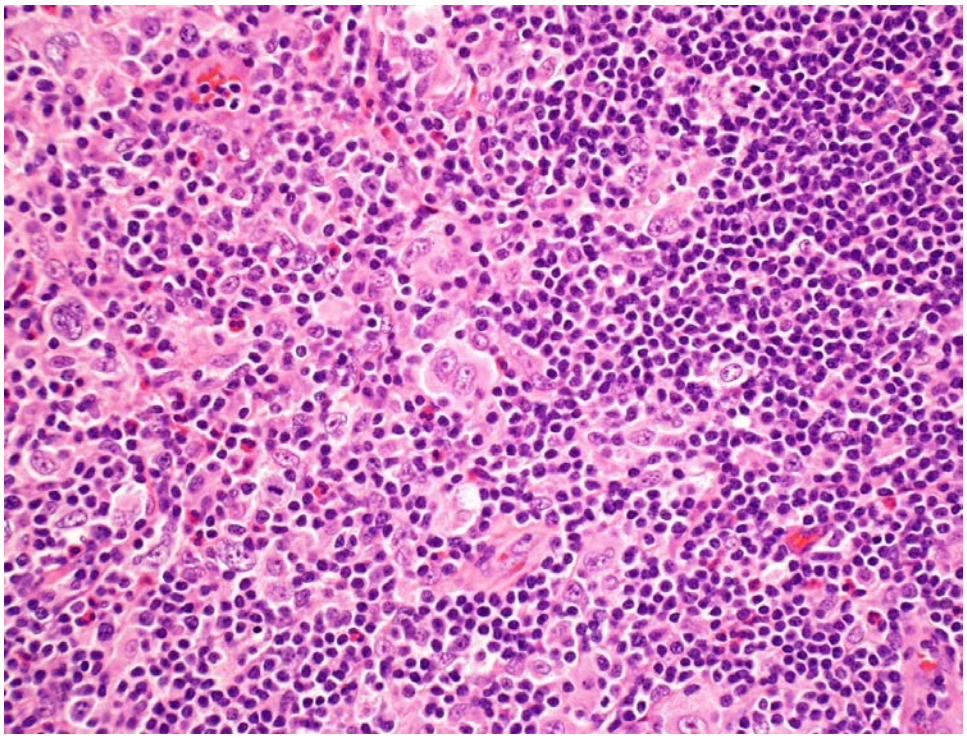

Figure 1a. CHL_40x

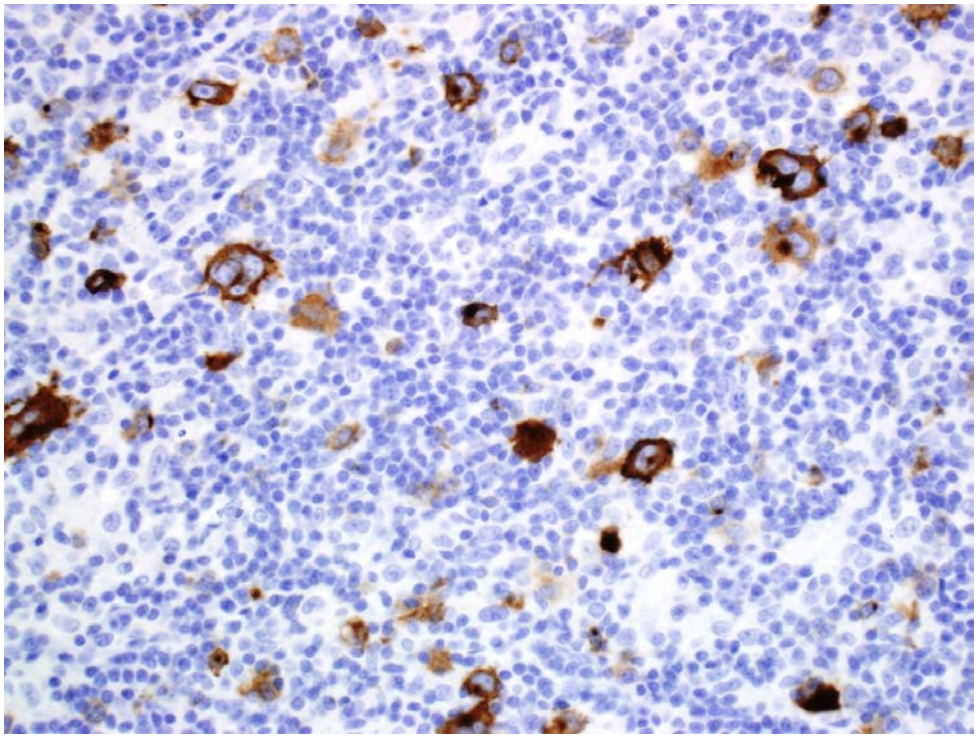

Figure 2b.CD30 x40

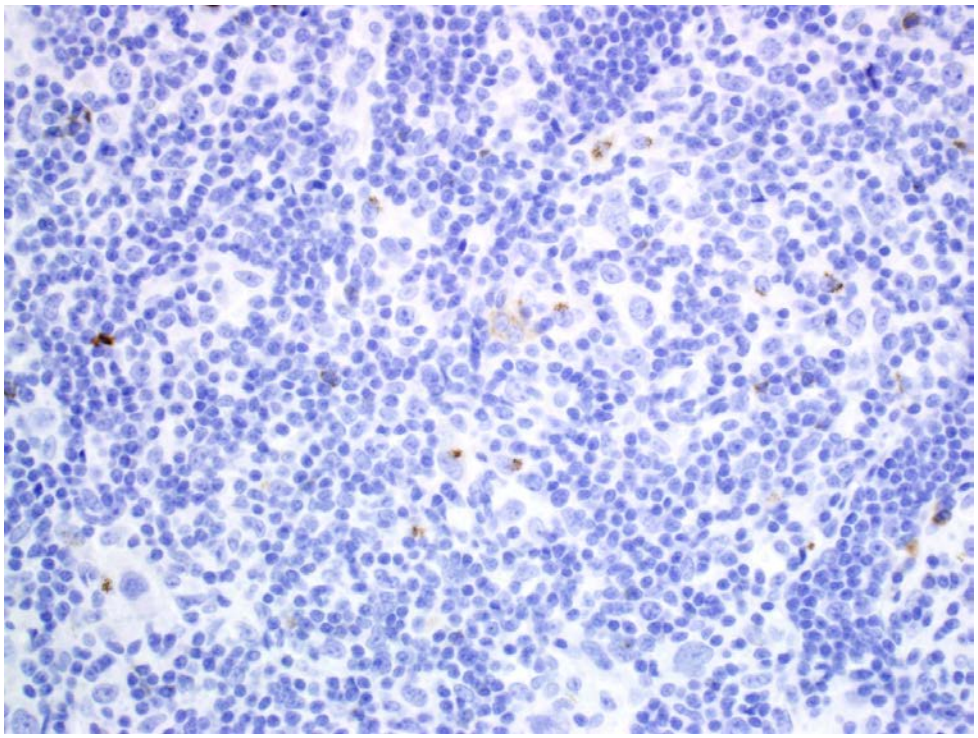

Figure 3c CD15_40X (002)

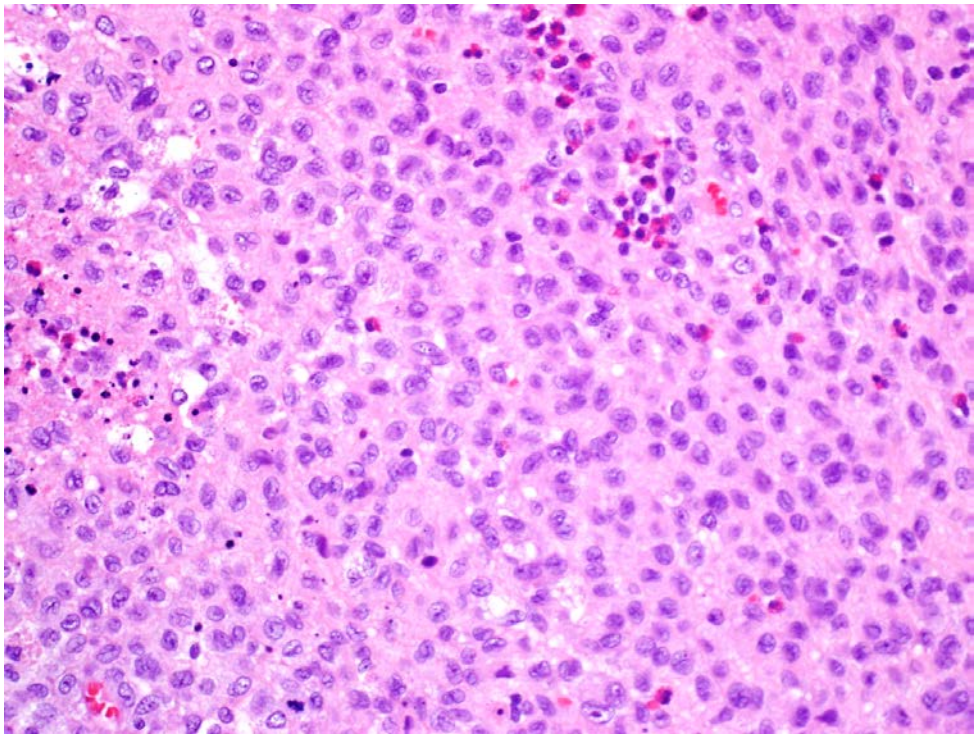

Figure 4d.40x

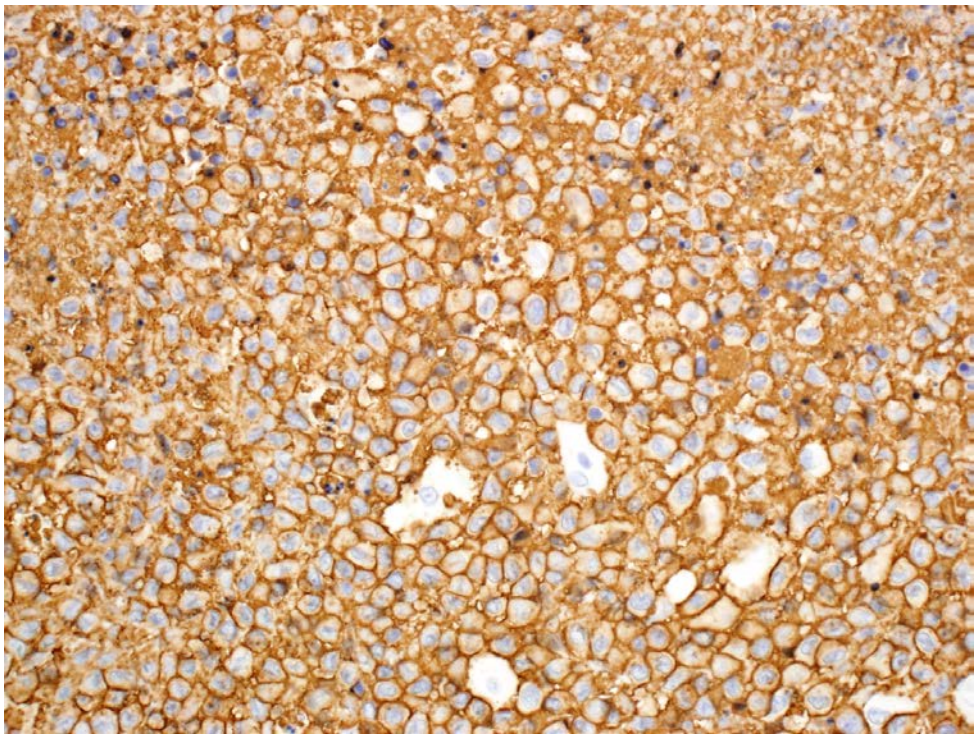

Figure 5e.CD1a x40

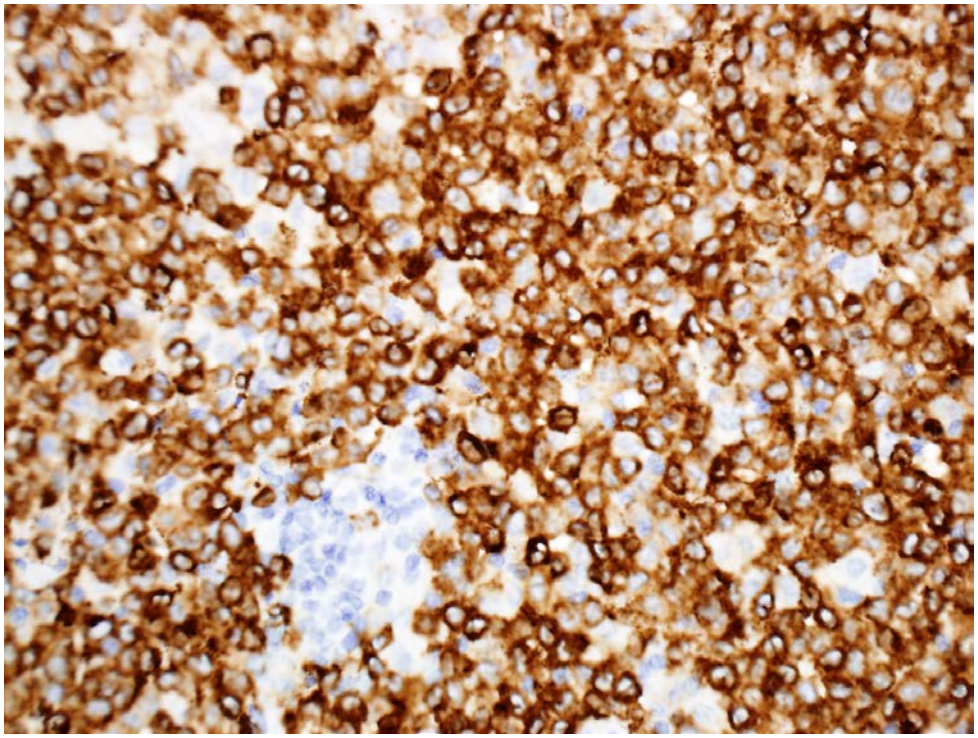

Figure 6f.Langerin x40

Final diagnosis: **N**odular sclerosis classic Hodgkin lymphoma (CHL) with foci of Langerhans cell histiocytosis (LCH)

Discussion:

This case demonstrated a concurrent involvement of a lymph node by CHL and LCH, which was exceedingly rare. It has been controversial if LCH associated with lymphoma represents a true neoplasm, highlighted by a recent finding that there were no *BRAF* or *MAP2K1* mutations in LCH. Our case may represent the first demonstration of *BRAF* V600E mutation in a typical case of LCH associated with lymphoma, supporting that at least some of the LCHs associated with lymphoma are true neoplasm. The twice-confirmed low allele frequency for the *BRAF* V600E mutation despite microdissection could point to an early clonal event in the background of an initially reactive Langerhans cell proliferation.

List of References

[1] H. Bosmuller, A. Fischer, D. L. Pham, T. Fehm, D. Capper, A. von Deimling, I. Bonzheim, A. Staebler, and F. Fend, "Detection of the BRAF V600E mutation in serous ovarian tumors: a comparative analysis of immunohistochemistry with a mutation-specific monoclonal antibody and allele-specific PCR," *Human pathology,* vol. 44, pp. 329-35, Mar 2013.

[2] L. J. Christie, A. T. Evans, S. E. Bray, M. E. Smith, N. M. Kernohan, D. A. Levison, and J. R. Goodlad, "Lesions resembling Langerhans cell histiocytosis in association with other lymphoproliferative disorders: a reactive or neoplastic phenomenon?," *Human pathology,* vol. 37, pp. 32-9, Jan 2006.

[3] A. L. Feldman, F. Berthold, R. J. Arceci, C. Abramowsky, B. M. Shehata, K. P. Mann, S. J. Lauer, J. Pritchard, M. Raffeld, and E. S. Jaffe, "Clonal relationship between precursor T-lymphoblastic leukaemia/lymphoma and Langerhans-cell histiocytosis," *The Lancet. Oncology,* vol. 6, pp. 435-7, Jun 2005.

[4] W. O. Greaves, C. Bueso-Ramos, and L. 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 : official journal of the American Society of Clinical Oncology,* vol. 29, pp. e76-8, Feb 1 2011.

[5] S. Pina-Oviedo, L. J. Medeiros, S. Li, J. D. Khoury, K. P. Patel, K. Alayed, R. C. Cason, C. J. Bowman, and C. C. Yin, "Langerhans cell histiocytosis associated with lymphoma: an incidental finding that is not associated with BRAF or MAP2K1 mutations," *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc,* vol. 30, pp. 734-744, May 2017.