

Nodal metastatic, undifferentiated nasopharyngeal carcinoma and classical Hodgkin lymphoma: Age old mimics

Editor,

A 37-year-old man presented with right sided neck swelling of 3 months duration. On examination, the patient had right levels II, III, V matted cervical lymph nodes and a left level III lymph node 1.5 cm × 1.5 cm. Computed tomography (CT) scan showed bilateral discrete cervical bulky lymph node enlargement, sizes 1-3 cm with a bulky retropharyngeal lymph node on the left side of 3 cm. CT chest, abdomen and pelvis were normal. Fine needle aspiration cytology of his cervical lymph node was done and showed scattered large, multinucleate tumor cells showing prominent nucleoli in a background of lymphocytes, histiocytes, and eosinophils [Figure 1a]. The cytology was suggestive of classical Hodgkin lymphoma. A lymph node biopsy was done. At very low magnification, a nodular pattern was observed due to a sclerosing stromal reaction arising from the capsule [Figure 1b]. At high power, binucleate cells resembling Hodgkin Reed Sternberg (HRS) cells were noted. The background showed a mixed inflammatory population of plasma cells, histiocytes and few eosinophils [Figure 1c]. Some of the tumor cells showed emperipolesis reminiscent of Rosai Dorfman disease [Figure 1d]. A few tumor cells resembled lacunar cells [Figure 1e]. The tumor cells were CD45 negative, CD20 negative, CD15 negative, CD163 negative, CD30 positive [Figure 1f] and positive for Epstein-Barr Virus (EBV) by EBV encoded RNA (EBER) transcript [Figure 1g]. The morphology and immunophenotype could both be compatible with classical Hodgkin lymphoma in this case. The mimicry that began in cytology and histopathology continued in immunohistochemistry. As immunostaining with CD30 did not show the distinct crisp cytoplasmic membrane and Golgi

staining one would expect to see in an HRS cell, Cytokeratin was done next. These large HRS like cells were all positive for cytokeratin [Figure 1h]. A diagnosis of metastasis from poorly differentiated carcinoma was given, and the clinician was advised to look for a primary in the nasopharynx. Indirect laryngoscopy was done and was normal. Rigid nasal endoscopy was done and showed a proliferative lesion confined to the posterior wall of nasopharynx which was bleeding on touch. A biopsy was taken from the same, and it was reported as nasopharyngeal carcinoma, undifferentiated type.

Diagnostic HRS cells must have at least two nucleoli in two separate nuclear lobes. In diagnostic HRS cells, the nuclei are large, often rounded in contour with irregular nuclear membrane, pale chromatin with one prominent eosinophilic nucleolus with perinuclear clearing (halo), resembling a viral inclusion. Mononuclear variants are termed Hodgkins cells.^[1] Antibodies against CD15, CD30, and CD20 are often used to support morphological diagnosis of classical Hodgkin's disease. The HRS

cells are CD15⁺, CD30⁺, and CD20⁻ in general with CD20 showing down regulation. If you look at the immunophenotypic profile of classical Hodgkin lymphoma in India, immunoreactivity for CD30 was almost a universal feature of classical Hodgkin lymphoma, seen in 99.74% of the cases. Half (49.11%) of the cases expressed CD15, whereas CD20 was expressed by 15.61% of the cases. None of the HRS cells expressed leukocyte common antigen (LCA) or CD3.^[2] The prevalence of EBV in the HRS cell varies according to the histological subtype and epidemiological features. The highest frequency (75%) is found in mixed cellularity classical Hodgkin lymphoma and the lowest incidence (10-40%) in nodular sclerosis classical Hodgkin lymphoma. In resource poor regions and in patients infected with the human immunodeficiency virus, EBV infection is more prevalent approaching 100%.^[1,3]

Nasopharyngeal carcinoma may present initially with cervical lymph node metastasis. The lymph nodes can be involved extensively or subtly. Some tumor cells can resemble HRS cells or lacunar cells, intermingled with a variable number of lymphocytes, plasma cells and eosinophils. Coupled with a dense lymphocytic infiltrate, a mistaken diagnosis of Classical Hodgkin Lymphoma is sometimes made. A desmoplastic stroma also may be present to mislead one further. The undifferentiated subtype is more common and is characterized by syncytial appearing large tumor cells with indistinct cell borders, round to oval vesicular nuclei and large central nucleoli. The tumor cells in nasopharyngeal carcinoma would be LCA negative, cytokeratin positive, CD30 positive and EBER positive. Nasopharyngeal carcinoma is associated with EBV in practically 100% of cases, irrespective of the ethnic background of the patient.^[4]

Epstein-Barr virus causes infectious mononucleosis and is also associated with a wide variety of malignancies other than classical Hodgkin lymphoma, which include non-Hodgkin lymphomas, posttransplant lymphoproliferative disorder, undifferentiated nasopharyngeal carcinoma, and gastric carcinoma. In biopsies, localization of EBER transcripts by *in situ* hybridization remains the gold standard for identifying latent infection.^[5] CD30 acts as a surrogate marker for EBV expression. Soluble CD30 has been detected in the sera of individuals infected with EBV, hepatitis B or C or human immunodeficiency virus. CD30 expression is detectable on large numbers of immunoblasts appearing during infectious mononucleosis and B-cells (and often T-cells) transformed by EBV. Human T-cell lymphotropic virus types I and II (HTLV-I, II) — infected lymphocytes and human natural killer-cell clones also express CD30. Both EBV and HTLV-I are powerful inducers of CD30 expression.^[6] Undifferentiated nasopharyngeal carcinoma and classical Hodgkin lymphoma can be both positive for CD30 and EBER as well as negative for CD45, CD20 and CD15. PAX5 and cytokeratin staining would help differentiate as the metastatic carcinoma cells would be negative for PAX5 and positive for cytokeratin, whereas the HRS cells would be positive for PAX5 and negative for cytokeratin. This case serves to illustrate the extreme degree to which undifferentiated type nasopharyngeal carcinoma can mimic classical Hodgkin lymphoma in nodal sites.

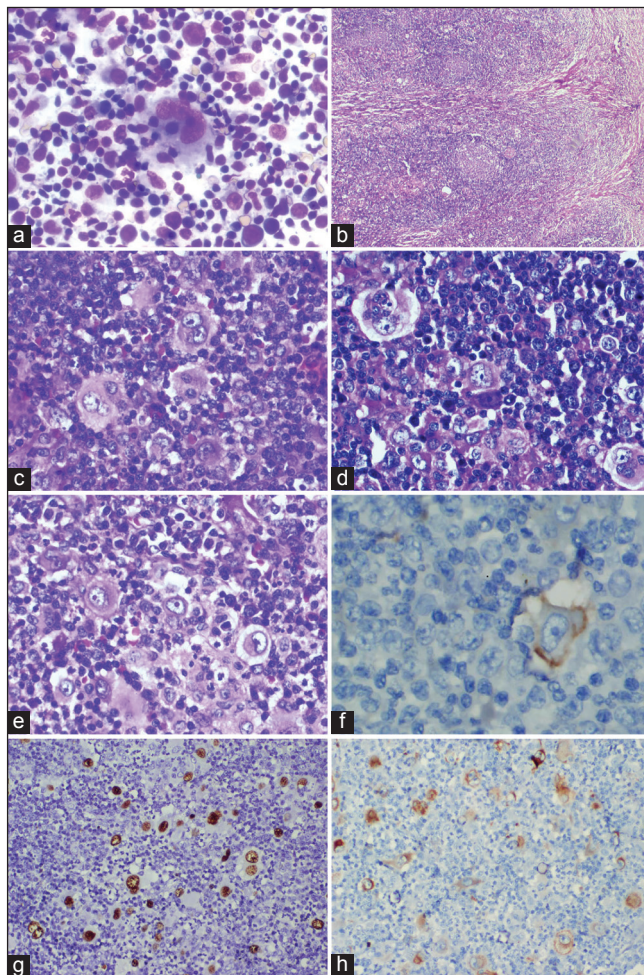


Figure 1: Cytology shows multinucleate cells in a polymorphous background. (b) Nodular pattern. (c) Binucleate Hodgkin Reed Sternberg cells. (d) Tumor cells showing emperipolesis. (e) Lacunar cells (f) tumor cells positive for CD30. (g) Tumor cells are positive for Epstein-Barr Virus by EBV encoded RNA transcript (h) tumor cells are positive for cytokeratin

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	DOI: 10.4103/0377-4929.138808