CASE REPORT

Unusual Histology in Hodgkin's Lymphoma: Report of an Interesting Case

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Abstract Hodgkin's lymphoma has a significant presence in the Indian subcontinent. Microscopically, the hallmark of Hodgkin's lymphoma (HL) is the Hodgkin and Reed-Sternberg (HRS) cell, which is usually surrounded by a cellular infiltrate of non-malignant inflammatory cells that constitute the majority of the tumor tissue. Cells which are known to be histologic mimics of HRS cells include immunoblasts, plasmablasts and rarely dendritic cells. We report a case of a 70-year-old male who presented with fever and lymphadenopathy. In the present case, the large cells with prominent nucleoli stained positively for both CD15 and CD30 and hence the possibility of angioimmunoblastic lymphadenopathy which was considered on the H&E-stained sections was excluded. In addition, noteworthy microscopic features in this case were angiogenesis and the presence of mast cells, both associated with a poor prognosis. The clinical impression was that of disseminated tuberculosis, but on histopathology, the final opinion was 'Hodgkin's lymphoma not classifiable with an unusual histology'. The aim of reporting this case is to highlight the unusual presentation in the form of prominent angiogenesis and mast cell infiltration in a case of HL, which is indicative of a poor prognosis.

Keywords Hodgkin's lymphoma · Unusual histology · Angioimmunoblastic lymphadenopathy · Disseminated tuberculosis

Introduction

The term 'Hodgkin's disease' was first coined by Samuel Wilks in honor of Dr. Thomas Hodgkin, who during his work as a pathologist at the Guy's Hospital, London, described young males who had died rapidly after a short fever-stricken illness with generalized lymphadenopathy [19]. The pathognomic microscopic feature of this disease, the Reed-Sternberg cell, was first described by Dorothy Reed and Karl Sternberg decades after the first descriptions of Hodgkin's lymphoma [13]. Presently, Hodgkin's lymphoma (HL) is classified into two largely distinct entities, namely nodular lymphocyte predominance HL (NLPHL) and classical HL (CHL), the latter being further subtyped as nodular sclerosis (NSCHL), lymphocyte-rich (LRCHL), mixed cellularity (MCCHL) and lymphocyte depletion (LDCHL) subtypes [9]. It has now been reported that angiogenesis and the presence of mast cells in the tumor tissue correlate with a poor prognosis [10, 12]. We report a case of a 70-year-old male who presented with fever and lymphadenopathy. The clinical impression was that of disseminated tuberculosis, but on histopathology, the final opinion was 'Hodgkin's lymphoma not classifiable with an unusual histology'.

Case Report

A 70-year-old male presented with complaints of loss of appetite and weight, generalized weakness and fever with night sweats since 4 months. He was admitted for further workup. The general condition of the patient was stable although he was anaemic with hemoglobin of 4 g% at the time of admission. Erythrocyte sedimentation rate (ESR) was raised and measured as 38 mm fall in the first hour by Wintrobe method. Complete blood count and peripheral smear showed severe

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anaemia of dimorphic type, for which he received three transfusions and the repeat hemoglobin levels reached 7.2 g/dL.

On general examination, an enlarged 1.5-cm-diameter left supraclavicular lymph node and mild hepatosplenomegaly were noted. Other relevant investigations included fine-needle aspiration cytology (FNAC) of the enlarged supraclavicular lymph node and imaging studies of the thorax and abdomen. Fine-needle aspirate yielded paucicellular smears with occasional epithelioid cell clusters and a mixed inflammatory infiltrate in a hemorrhagic background. The possibility of a granulomatous lesion was considered. Contrast-enhanced computed tomography (CECT) thorax and abdomen showed mediastinal, cervical, axillary and abdominal lymphadenopathies along with hepatomegaly and splenomegaly with ill-defined hypodense hypoenhancing area in splenic parenchyma ?small abscess/infarct (Fig. 1). Based on these investigations, a provisional diagnosis of disseminated tuberculosis was made and the enlarged lymph node was biopsied for confirmation. Microscopic examination showed an effaced lymph node architecture (Fig. 2). Arborizing thin-walled capillaries with a mixed inflammatory infiltrate of lymphocytes, plasma cells, eosinophils and scattered mast cells were seen throughout the sections (Fig. 3). Numerous atypical mononuclear cells with high *N/C* ratio and prominent eosinophilic nuclei were seen. Very rare binucleate cells with a Reed–Sternberg-like morphology were seen and also many immunoblast-like cells (Fig. 2). Few epithelioid cell clusters were seen. No well-formed granuloma or areas of necrosis were seen. The possibilities considered were Hodgkin's

Fig. 1 Photomicrograph of CECT thorax and abdomen showing mediastinal and abdominal lymphadenopathies along with hepatomegaly and splenomegaly with ill-defined hypodense hypoenhancing area in splenic parenchyma ?small abscess/infarct

Fig. 2 Photomicrograph showing complete effacement of lymph node architecture (hematoxylin and eosin, $\times 100$). *Inset top right*—atypical mononuclear cells with prominent eosinophilic nuclei against a polymorphous population (hematoxylin and eosin, $\times 100$); *inset bottom right*—CD30-positive atypical large cells

lymphoma or angioimmunoblastic lymphadenopathy in an elderly male, and immunohistochemical studies and special stains were done for further confirmation. A panel of immunohistochemical stains was put up. The large cells were positive for both CD15 and CD30 markers (Fig. 2) in a background of a polymorphous lymphocytic milieu which did not take up the CD15 or CD30 immunostaining whereas CD20 staining was negative throughout the sections. Immunohistochemical staining for endothelial cells with CD31 showed many microvessels which were a very striking feature in this case (Fig. 3). Also, modified Giemsa stain was done which highlighted the presence of mast cells in the sections (Fig. 3). In view of these findings, a final diagnosis of Hodgkin's lymphoma (not classifiable) with unfavorable

Fig. 3 Photomicrograph showing arborizing thin-walled capillaries with a mixed inflammatory infiltrate of lymphocytes, plasma cells, eosinophils and scattered mast cells (hematoxylin and eosin, $\times 400$). *Inset top left*—Giemsa-positive mast cells (modified Giemsa, $\times 100$); *inset bottom left*—CD31 positivity in blood vessels

histology in the form of prominent angiogenesis and mast cells was offered. The patient was referred to the regional government oncology centre for chemotherapy and further management.

Discussion

Hodgkin's lymphoma has a significant presence in the Indian subcontinent. The Globocan project (under the aegis of the International Agency for Research on Cancer) provides contemporary estimates of the incidence, mortality and prevalence of major types of cancer for 184 countries of the world. For the year 2012, it reported the incidence of HL among Indian males as 5677 per 100,000 and 2938 per 100,000 in Indian females and in terms of mortality for HL, 2938 males per 100,000 died and 1404 per 100,000 females died [5]. Microscopically, the hallmark of HL is the Hodgkin and Reed-Sternberg (HRS) cells; these are usually surrounded by a cellular infiltrate of non-malignant inflammatory cells that constitute the majority of the tumor tissue. HRS cells have now been identified as clonal B cells that lack typical B cell surface antigens. B cells failing to express surface immunoglobulin usually undergo apoptosis; however, HRS cells escape cell death through a number of mechanisms, most importantly incorporation of Epstein-Barr virus (EBV) latent membrane proteins (LMP1 and 2) and also interaction with components of the microenvironment [18, 20]. Detection of EBV by EBV-encoded RNA (EBER) transcript localization by in situ hybridization is regarded as the gold standard for identifying latent infection [6]. This investigation however could not be done in the present case due to financial constraints. FNAC is an important diagnostic modality used universally in the initial assessment of enlarged and palpable lymph nodes. The reported accuracy for the diagnosis of Hodgkin's lymphoma by fine-needle aspiration differs markedly in different studies. Various Indian studies have reported values ranging from 30 to 92% of Hodgkin's lymphoma that were correctly diagnosed in large series of lymph node FNACs [2, 14]. The wide range of cytologic features seen in HL reflects the histological diversity of the disease and also coincides considerably with other reactive lesions, often leading to problems in diagnosis. False-negative diagnoses can be attributed to either poor technique, partial involvement of the node, obscuring reactive inflammatory cells, fibrosis, infrequent diagnostic Reed-Sternberg cells and the presence of poorly formed granulomas with histiocytic collection [1, 15]. In the present case, FNAC of the enlarged supraclavicular lymph node showed a few epithelioid cells in a polymorphous background which led to a suspicion of tuberculosis.

Rye classification has been widely used for many years. In the Revised European-American Lymphoma or World Health Organization (REAL/WHO) classification,

the 'lymphocyte-rich, classical Hodgkin's lymphoma' category was added [20]. The commonest type of HL is nodular sclerosis (NSHL) which accounts for >50% (up to 80%) of cases. Unclassifiable cases used to be placed in the mixed cellularity category [11], but the REAL/WHO classification recommends labeling such cases as 'HL not classifiable' [7]. Older age has been typically identified as an independent adverse prognostic indicator for HL survival in population-based studies, the over 60-year age group accounting for approximately 20% of cases of HL [17]. Our patient was a 70-year-old male; other unfavorable parameters in this case as outlined by the German Hodgkin's Study Group included presence of large mediastinal adenopathy and involvement of more than three lymph node sites on imaging and ESR > 30 mm fall in the first hour with B symptoms (fever with night sweats and unexplained weight loss) [3].

Cells which are known to be histologic mimics of HRS cells include immunoblasts, plasmablasts and rarely dendritic cells [16]. In the present case, the large cells with prominent nucleoli stained positively for both CD15 and CD30 and hence the possibility of angioimmunoblastic lymphadenopathy which was considered on the H&E-stained sections was excluded. In addition, noteworthy microscopic features in this case were angiogenesis and the presence of mast cells, both associated with a poor prognosis [10, 12]. Molin et al. have proposed that mast cells produce functionally active CD30 ligand (CD30L) which stimulates HRS cells leading to a poor prognosis [12]. It has been claimed that immunostaining with CD31 is a good differentiator between blood and lymphatic vessels in lymph nodes [8]. CD31 staining was done in this case, and a fine network of microvessels was delineated. Also, modified Giemsa stain helped to identify mast cells in the sections, which was another special feature of this case. Glimelius et al. estimated the number of microvessels immunohistochemically stained for CD31, in which three to five fields with the highest concentration of blood vessels (hotspots) were counted and then statistically analysed. They found that in univariate analyses, HL patients with a high microvessel count had a worse progression-free survival as compared with those with a lower number of microvessels. They also speculated that the higher number of microvessels in elderly patients may indicate a biological difference between HL in younger and older patients [4].

Conclusion

In conclusion, HL has a histologically diverse microscopic picture not always conforming to the distinct entities as classified under the Rye or REAL/WHO classification. Unusual histologic features like the presence of mast cells and

microvessels, as seen in the present case, serve as an indication of a poor prognosis in Hodgkin's lymphoma.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

- Chhieng DC, Cangiarella JF, Symmans WF, Cohen JM (2001) Fine needle aspiration cytology of Hodgkin disease. A study of 89 cases with emphasis on the false-negative cases. *Cancer Cytopathology* 93(1):52–59
- Das DK, Gupta SK, Datta BN, Sharma SC (1990) Fine needle aspiration cytodiagnosis of Hodgkins disease and its subtypes. I Scope and limitations *Acta Cytol* 34:329–336
- Eich HT, Diehl V, Gorgen H, Pabst T, Markova J, Debus J et al (2010) Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. *J of Clin Oncol* 28(27):4199–4206
- Glimelius I, Edström A, Fischer M, Nilsson G, Sundstrom C, Molin D et al (2005) Angiogenesis and mast cells in Hodgkins lymphoma. *Leukemia* 19:2360–2362
- Globocan 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. <http://globocan.iarc.fr/Default.aspx>
- Gulley ML, Tang W (2008) Laboratory assays for Epstein-Barr virus-related disease. *J Mol Diagn* 10:279–292
- Harris NL (1999) Hodgkins disease: classification and differential diagnosis. *Mod Pathol* 12:159–175
- Hattori H (2003) Caution should be taken in using CD31 for distinguishing the vasculature of lymph nodes. *J Clin Pathol* 56: 638–639
- Jaffe ES, Harris NL, Stein H, Vardiman J (2001) Pathology and genetics of tumours of haematopoietic and lymphoid tissues. IARC Press, Lyon, France
- Korkolopoulou P, Thymara I, Kavantzias N, Vassilakopoulos TP, Angelopoulou MK, Kokoris SI et al (2005) Angiogenesis in Hodgkin's lymphoma: a morphometric approach in 286 patients with prognostic implications. *Leukemia* 19:894–900
- Lukes RJ (1971) Criteria for involvement of lymph node, bone marrow, spleen and liver in Hodgkins disease. *Cancer Res* 31: 1755–1767
- Molin D, Edstrom A, Glimelius I, Glimelius B, Nilsson G, Sundstrom C et al (2002) Mast cell infiltration correlates with poor prognosis in Hodgkin's lymphoma. *Br J Haematol* 119:122–124
- Mukherjee, S. (2010). Part 2: an impatient war an anatomist's tumor, In: Anonymous pp. 151–161, Scribner, A division of Simon & Schuster, Inc, 978–1–4391-0795-9, New York, NY
- Prasad RR, Narasimhan R, Sankaran V, Velith AJ (1996) Fine needle aspiration cytology in the diagnosis of superficial lymphadenopathy: an analysis of 2,418 cases. *Diagn Cytopathol* 15:382–386
- Rajalakshmi T, Rashmi Kumari TR (2008) Fine needle aspiration cytology in the diagnosis of Hodgkins lymphoma: hits and misses. *J of Cytol* 25(1):10–12
- Sidawy Mary K, Ali Syed Z (2007) Fine needle aspiration cytology a volume in foundations in diagnostic pathology. Elsevier Health Sciences. pages 81–82
- Stark GL, Wood KM, Jack F, Angus B, Proctor SJ, Taylor PR et al (2002) Hodgkins disease in the elderly: a population based study. *Br J Hematol* 119:432–440
- Steidl C, Connors JM, Gascoyne RD (2011) Molecular pathogenesis of Hodgkins lymphoma: increasing evidence of the importance of the microenvironment. *J Clin Oncol* 29(14):1812–1826
- Stone, M. J. (2010). Samuel Wilks: the “grand old man” of British medicine. *Proc. (Bayl Univ. Med. Cent)*, Vol. 23, No. 3,(Jul), pp.263–265, 0899–8280; 0899–8280
- Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. (2008) Hodgkins lymphoma. WHO classification of tumours of hematopoietic and lymphoid tissues, 4th Edition. International Agency for Research on Cancer