Original Article

Hodgkin Lymphoma in Pediatric Patients with Unusual Cytologic Findings

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Abstract

Background: Background: Cytologic findings of classic Hodgkin lymphoma are highly characteristic; very large Reed–Sternberg cells or their mononuclear variants, the Hodgkin cells (HRS cells), stand out against a reactive background. Aims and Objectives: To study the cytological features of Hodgkin lymphoma in paediatric patients, with special emphasis on unusual cytologic findings.

Materials and Methods: Seven paediatric lymph node cases of Hodgkin lymphoma, in the age range of 0–12 years, were included in this retrospective study. Outcomes were compared with results of subsequent histopathology.

Results: Seven cases were diagnosed as Hodgkin lymphoma on fine needle aspiration cytology (FNAC), with ages ranging from 4 to 7 years. All were male patients. Eosinophilia in peripheral blood smear was present in two out of seven cases (28.57%). Eosinophils in FNAC smears were seen in six out of seven cases (85.71%). The neoplastic cells were mononuclear, binucleate (classic Reed–Sternberg), multinucleated, multilobated, and Popcorn cells. Unusual characteristics observed among RS cells of Hodgkin lymphoma included: Presence of germinal centre cells, Presence of bare/naked nuclei, Emperipolesis, Crushing artefact causing differential diagnosis of anaplastic large cell lymphoma (ALCL)

Conclusion: Although Hodgkin lymphoma exhibits characteristic cytologic findings, unusual features may also be present, as highlighted in this study. When these atypical findings are the only ones observed in cytology smears, a careful search for RS cells is essential to avoid misdiagnosis.

Keywords:

Eosinophilia, FNAC, Hodgkin lymphoma, Paediatric, Reed–Sternberg cells

Introduction

Fine needle aspiration cytology (FNAC) is reported to have a higher accuracy in diagnosing Hodgkin lymphoma (HL) (91.8%) [1]. Classic Reed–Sternberg cells are bilobed, binucleated, or multinucleated cells with abundant cytoplasm and prominent macronucleoli [2].

Classic Hodgkin's lymphoma frequently shows mononuclear cells with nuclear structures similar to typical Reed–Sternberg cells

(mononuclear Hodgkin cells) along with their bare nuclear forms [3].

Hodgkin lymphoma is classified into: I) Classical Subtypes: Nodular Sclerosis, Mixed Cellularity, Lymphocyte-rich, Lymphocyte-depleted. II) Lymphocyte Predominant [4].

Aims and Objectives

To study the cytological features of Hodgkin lymphoma in paediatric patients, with special emphasis on unusual cytology findings.

Materials and Methods

Seven paediatric lymph node cases of Hodgkin lymphoma, in the age range of 0-12 years, were included in this retrospective study from January 2011 to December 2013. Clinical findings and peripheral blood smear findings were noted. For all the patients, informed written consent was obtained from the patient's parent/guardian. Material was obtained by a non-aspiration technique using a sterile disposable needle (23-25 gauge and 3-5 cm long) attached to a 10 ml disposable syringe. The air-dried slides, fixed in methanol, were stained with Giemsa, and the wet-fixed slides (fixed for 30 minutes in absolute alcohol) were stained with Papanicolaou stain (PAP) and examined. The outcome was compared with the results of subsequent histopathology.

Results

We diagnosed seven cases of Hodgkin lymphoma through fine needle aspiration cytology (FNAC), with patients aged between 4 and 7 years. All patients were male. Six cases presented with cervical lymphadenopathy, while inguinal lymphadenopathy was observed in one case.

Peripheral Blood Findings: Eosinophilia was detected in two out of seven cases (28.57%), with absolute counts of 624 and 1044 cells/μL.

Cytology Findings: Smears revealed mature and transformed lymphocytes, histiocytes, and plasma cells. Two cases showed germinal center cells [Figure 1b], suggesting incomplete nodal architecture replacement by lymphoma. Eosinophils were observed in six out of seven cases (85.71%) [Figure 1d].

Neoplastic cells were mononuclear [Figure 1a], with moderate cytoplasm and a large, round nucleus containing a macronucleolus (one-fourth the size of the nucleus). Binucleate cells (classic Reed-Sternberg), multinucleated, multilobated [Figure 1b], and popcorn cells [Figure 1c] were also present.

Histopathological examination of Hodgkin lymphoma revealed effaced lymph node architecture infiltrated by a heterogeneous population of lymphocytes, eosinophils, macrophages, plasma cells, mononuclear, and classic Reed-Sternberg (RS) cells [Figure 1e].

Immunohistochemistry (IHC): RS cells were CD30+ and CD15+.

Unusual Characteristics Observed in RS Cells: Presence of bare/naked nuclei, Emperipolesis, Crushing artifact, raising the differential diagnosis of anaplastic large cell lymphoma (ALCL)

Hodgkin Lymphoma with Bare/Naked Nuclei: Age/Gender: 4.5 years, Male. Presentation: Inguinal, multiple, discrete, non-tender, firm lymph nodes with restricted mobility (largest 3 × 3 cm) for 2 months.

Cytology Findings: Smears revealed mature and transformed lymphocytes, eosinophils, plasma cells, histiocytes, mononuclear,

binucleate, multilobated, and popcorn cells. Cells had moderate cytoplasm, large round nuclei with macronucleoli (one-fourth the size of the nucleus), and numerous bare/naked nuclei [Figure f]. Diagnosis: Nodular sclerosis variant of Hodgkin lymphoma confirmed by biopsy.

Hodgkin Lymphoma with Emperipolesis: Age/Gender: 7 years, Male. Presentation: Left axillary, multiple, discrete, mobile, non-tender, soft lymph nodes (largest 3 × 3 cm) for 2 years.

Cytology Findings: Mature and transformed lymphocytes, eosinophils, and mononuclear cells with moderate cytoplasm and large round nuclei. Macronucleoli were one-fourth the size of the nucleus. Binucleate, multilobated, and popcorn cells exhibited emperipolesis [Figure 1g]. Diagnosis: Classic Hodgkin lymphoma, mixed cellularity, confirmed histopathologically.

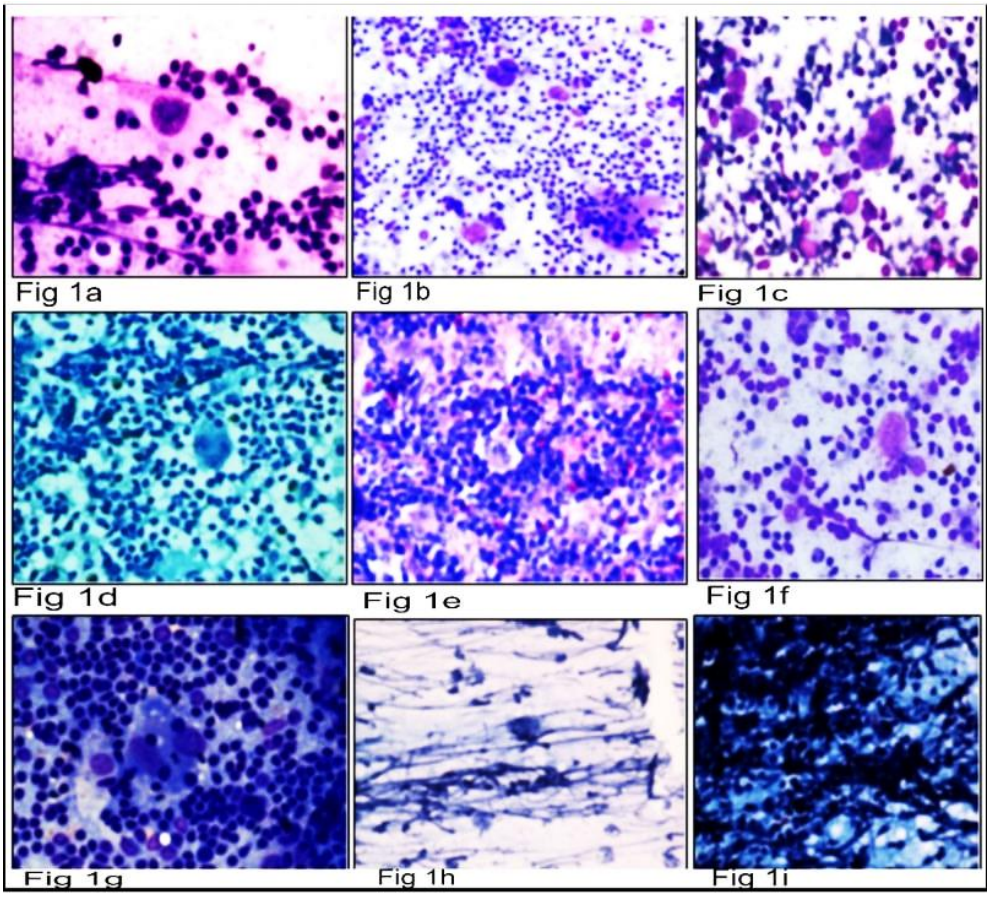

Figure 1: Mononuclear cell (a), mononucleate, binucleate, and multilobated germinal centre cells (b), popcorn cell (c), eosinophils (d), RS cell and eosinophils in histology (e), bare nuclei and plasma cell (f), emperipolesis in Hodgkin Lymphoma (g), RS cell mimicking hallmark cell of ALCL (h), and crush artifact (i) with respective stains and magnifications.

Hodgkin Lymphoma with Features Resembling ALCL: Age/Gender: 5 years, Male. Presentation: Right level IB, multiple, discrete, non-tender, firm lymph nodes with restricted mobility (largest 1.5 × 1 cm) for 2 months.

Cytology Findings: Smears showed mature and transformed lymphocytes, with a few large cells exhibiting pale, abundant cytoplasm and large nuclei. Some cells were binucleate and multinucleate with macronucleoli. Crushing artifacts created pleomorphic appearances, resembling hallmark cells of ALCL [Figure 1h, 1i].

Differential Diagnoses: Hodgkin lymphoma, ALCL, Histopathological Diagnosis: Classical Hodgkin lymphoma. IHC: Large cells were CD30+, CD15+, and Pax5 (weak+).

Histopathological Follow-up: All cases were confirmed as Hodgkin lymphoma through biopsy: Mixed cellularity – 5 cases (71.42%), Nodular sclerosis – 1 case (14.29%), Classical variant (not further subclassified) – 1 case (14.29%)

Discussion

Fine Needle Aspiration Cytology (FNAC) is a widely used technique for evaluating lymph nodes in the diagnosis of lymphomas. Along with immunophenotyping and molecular studies, it is accepted in many centers as an initial diagnostic tool. The cornerstone of cytodiagnosis for Hodgkin lymphoma is the identification of classic Reed-Sternberg/Hodgkin cells in a polymorphous cellular background. The broad spectrum of cytologic features in Hodgkin lymphoma reflects the histological diversity of the disease but overlaps significantly with reactive and malignant lesions, complicating diagnosis [5].

Miliauskas notes that large, multilobated nuclei resembling Reed-Sternberg cells can appear in various conditions. Atypical immunoblasts in non-neoplastic reactive lymphadenopathy—such as in mononucleosis, toxoplasmosis, rheumatoid arthritis, and drug-induced lymphadenopathy—may present with such nuclei. However, these typically differ from Reed-Sternberg cells by having smaller, darker nucleoli, denser chromatin, and basophilic cytoplasm. Multinucleated giant cells in small or large cell non-Hodgkin lymphoma, including lymphoplasmacytic lymphoma, Peripheral T-cell Lymphoma (PTCL) NOS, and especially ALCL or T-cell rich B-cell lymphoma, may also exhibit large nucleoli similar to Reed-Sternberg cells. Distinguishing between these becomes particularly challenging in the presence of eosinophils, plasma cells, and epithelioid cells, which are not uncommon in T-cell lymphoma [3].

In a study by Chhieng et al., the male-to-female ratio was 49:23, while in our study, all seven patients were male, reinforcing the male predominance in Hodgkin lymphoma [6].

Hodgkin Lymphoma and Eosinophils: Eosinophils play an important role in the pathobiology of Hodgkin lymphoma. Although the mechanism of eosinophilia remains unclear, mediators such as Interleukin-5 and Granulocyte Monocyte-Colony Stimulating Factor (GM-CSF) have been implicated. The role of eosinophils in Hodgkin lymphoma has been unequivocally established. Eosinophils may contribute to the pathology by acting as cellular ligands for Tumor Necrosis Factor-superfamily receptors (CD40, CD30, CD95/Fas), which can transmit proliferative and anti-apoptotic signals to Reed-Sternberg cells [7].

Eosinophilia is defined as the presence of >500 eosinophils per µL of blood [8]. A study by Cyriac et al. reported an eosinophilia incidence of approximately 15% in Hodgkin lymphoma. Both peripheral and tissue eosinophilia are observed in Hodgkin lymphoma [7]. In our study, tissue eosinophilia was present in 85.71% of FNAC smears, and peripheral blood eosinophilia was detected in 28.57%.

Miliauskas describes the nodular lymphocyte-predominant subtype as featuring a monotonous population of slightly irregular small lymphocytes with scattered large pale multinucleated giant cells, corresponding to ‘popcorn’ cells in histology, typically without distinct nucleoli [3]. In our study, popcorn cells were observed in five cases of Hodgkin lymphoma, which histopathology revealed as mixed cellularity (four cases) and nodular sclerosis (one case). No literature supporting this finding was found.

Hodgkin Lymphoma and Bare Nuclei: A case of Hodgkin lymphoma, confirmed as the nodular sclerosis variant on biopsy,

revealed many mononuclear cells without cytoplasm, along with mononucleate and binucleate cells.

Miliauskas states that classic Hodgkin lymphoma often shows mononuclear cells with nuclear features similar to Reed-Sternberg cells (mononuclear Hodgkin cells) and their bare nuclear forms. In such cases, a definitive diagnosis requires histological examination, except in recurrent disease when classic Reed-Sternberg cells are unnecessary for diagnosis [3].

In the nodular sclerosis variant, lacunae around lacunar cells result from formalin fixation shrinkage artifacts and are not seen in cytologic preparations but may appear in cell block sections. However, Hodgkin-Reed-Sternberg (HRS) cells in nodular sclerosis Hodgkin lymphoma typically have smaller nuclei, smaller nucleoli, and more abundant cytoplasm than in other subtypes [2]. This case highlights the presence of many bare nuclei, a known feature of classic Hodgkin lymphoma.

Hodgkin Lymphoma and Emperipolesis: One case in our study demonstrated emperipolesis in neoplastic cells of mixed cellularity Hodgkin lymphoma. Di Lu et al. described four malignant lymphoma cases (two low-grade follicular lymphoma and two Hodgkin's disease) showing focal sinus histiocytosis with massive lymphadenopathy (SHML) [9,10]. Maia et al. also observed this in two Hodgkin's disease cases, all of which were nodular lymphocyte-predominant type [10]. More recently, sinus histiocytosis has been reported as a focal finding in lymph nodes involved in mixed cellularity Hodgkin lymphoma [10].

Falk et al. identified emperipolesis in two Hodgkin lymphoma cases [11]. Although rare, emperipolesis is more frequently associated with non-Hodgkin lymphoma than Hodgkin lymphoma [12].

ALCL versus Hodgkin Lymphoma: Anaplastic Large Cell Lymphoma (ALCL) hallmark tumor cells can be multinucleated and resemble Reed-Sternberg cells. In our study, a crushing artifact led to Reed-Sternberg cells mimicking ALCL hallmark cells. As a result, a differential diagnosis of ALCL versus Hodgkin lymphoma was considered, but biopsy confirmed Hodgkin lymphoma [13].

Presence of Germinal Center Cells: In two cases, germinal center cells were noted. Partial lymph node involvement by Hodgkin lymphoma can yield false negatives in FNAC smears. Rashmi Kumari et al. reported that one of two false-negative cases was likely due to focal lymph node involvement [5].

However, in our cases, neoplastic cells were present, and no false negatives were reported.

Histopathological Correlation: Chhieng et al. reported 57.5% nodular sclerosis, 24.7% mixed cellularity, 6.8% lymphocytic depleted, and 2.7% lymphocytic predominance. Six cases (8.3%) were not further classified due to core biopsy limitations [6]. In our study, mixed cellularity predominated (71.42%), followed by nodular sclerosis (14.29%) and an unclassified classical variant (14.29%).

The predominance of mixed cellularity aligns with younger populations (0-12 years), contrasting with Chhieng et al.'s study, which included ages 5 to 90 years [14].

Conclusion

Although Hodgkin lymphoma has characteristic cytological features, unusual findings may occasionally appear. This study emphasizes the importance of careful examination to identify Reed-Sternberg cells, minimizing the risk of misdiagnosis.

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