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Hodgkin lymphoma with an interfollicular growth pattern: A clinicopathologic study of 8 cases

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ABSTRACT

Classic Hodgkin lymphoma (CHL) has four subtypes. Different morphologic variations can be seen in lymph nodes involved by CHL. Primary interfollicular (IF) involvement is not considered a separate subtype but an unusual diagnostically challenging morphologic variant. Our aim was to study the prevalence of IF growth pattern and coexistence of other morphologic variants in lymph nodes involved by CHL, to investigate the diagnostic challenges and clinical importance of this growth pattern, and to find helpful histologic clues in cases with subtle morphologic features to help avoid misinterpretation and missed diagnosis. We performed a retrospective review study over 10 years. We searched for diagnosed cases of nodal CHL. We retrieved and reviewed cases of CHL with IF involvement. The clinical and pathologic features of each case were collected and compared. We found 103 cases of CHLs. Eight cases (7.8%) demonstrated IF growth patterns. The age range was between 3 and 48 years with an average age of 26 years. The male to female ratio was 7:1. Six cases were mixed cellularity HLs. Three cases had associated epithelioid granulomas, one had follicular involvement and one had an associated. HHV-8 negative plasma cell rich Castleman disease. One case was initially missed as benign follicular hyperplasia, one case was referred as CD and three cases were initially suspected as HL. IF growth pattern in nodal CHLs can be missed because it can be mild and focal with subtle morphologic features. The presence of epithelioid histiocytes, eosinophils and other coexistent morphologic variants are helpful histologic clues. In doubtful cases, immunohistochemistry study is essential. The majority were early stage cervical node MCHLs in young adults and children. Pathologists should be aware of this possibility when examining reactive lymph nodes. The clinical significance is limited and needs further validation by larger studies.

1. Introduction

Classic Hodgkin lymphoma (CHL) is divided into four subtypes: nodular sclerosis, mixed cellularity, lymphocyte rich and lymphocyte depleted [1]. The diagnostic hallmark of CHL is the recognition of Reed-Sternberg (RS) cells in a mixed inflammatory background with the appropriate immunophenotype [1-4]. There are morphologic variations in lymph nodes involved by CHL that do not constitute a subtype. They include foamy macrophages sometimes forming xanthogranulomatous reaction, eosinophilia, follicular involvement mimicking follicular lysis, progressive transformation of germinal centers, fibrosis, necrosis, non-caseating epithelioid sarcoid-like granulomas, Castleman disease (CD)-like changes and spindle cell proliferation mimicking sarcomas [1-4]. Unawareness of these histomorphologic variations may result in mistaken diagnoses. Focal involvement of the lymph node with paracortical and interfollicular distribution between hyperplastic lymphoid follicles has been recognized as a focal or early interfollicular involvement in CHL [5-11]. It is not considered as a specific subtype. It is categorized in the 2008 classification of the World Health Organization as a morphologic pattern that is most commonly seen in mixed cellularity HLs (MCHL) [1]. Probably, Lennert, in 1958, was the first to describe Hodgkin lymphoma in its early involvement of only a small part of the lymph node [5]. Strum and Rappaport emphasized the significance of IF involvement in lymph nodes in 1970 [6]. In 1971, Lukes also recognized this pattern that constitutes a peculiar form of focal involvement, but not a new entity [7]. The subtle morphologic features might result in missed diagnosis. The coexistence of other morphologic variations might further complicate the situation by overmasking the limited IF involvement. We performed a retrospective review study to investigate the prevalence, diagnostic challenges, potential histologic clues and the clinical importance of IF growth patterns in nodal CHLs.

2. Materials and methods

We used a computer-based search to retrieve all of the cases of CHLs that were diagnosed in our institution over the past 10 years from 2008

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Table 1
Clinical features of the patients diagnosed with classic Hodgkin lymphoma with primary interfollicular involvement.

SN	Age	Sex	Clinical presentation	Biopsy site/ radiology/stage	Treatment	Follow up
1	16	M	Right neck swelling × 2 months No B-symptoms ESR = 4	Right cervical LN Cervical & axillary LA Stage IIA	Chemotherapy	11 years, developed generalized LA and HSM, diagnosed TCRBCL, died
2	26	M	Right neck swelling × 2 months No B-symptoms ESR = 24	Right cervical LN Right cervical LA Stage IB	Chemotherapy	4 years, no recurrence
3	3	M	Right neck swelling × 3 weeks Fever ESR = 125	Right cervical LN Cervical and mediastinal LA Stage IIB	Chemotherapy	8 years, no recurrence
4	48	M	Left neck swelling × 1.5 month Weight loss ESR = 25	Left cervical LN Left cervical LA Stage IIB	Chemotherapy Radiotherapy	5 years, no recurrence
5	34	M	Left neck swelling × 1 month No B-symptoms ESR (NA)	Left cervical LN Left cervical LA Stage IA	Chemotherapy Radiotherapy	4 years, no recurrence
6	7	M	Left neck swelling × 1 month No B-symptoms ESR = 26	Left cervical LN Left cervical LA NA	Not received (missed initial diagnosis)	After 2 years developed generalized LA and HSM with B-symptoms and ESR = 120, cervical LN biopsy showed NSHL, alive
7	40	F	Right neck swelling × 3 weeks No B-symptoms ESR = 21	Right cervical LN Bilateral cervical LA Stage IIA	NA	No follow up
8	31	M	Fatigue, dizziness, anemia and generalized LA × 1 month ESR (NA)	Left cervical LN NA NA	NA	No follow up

SN: serial number, M: male, LN: lymph node, LA: lymphadenopathy, HSM: hepatosplenomegaly, TCRBCL: T-cell rich B-cell lymphoma, ESR: erythrocyte sedimentation rate, NA: not available, F: female, NSHL: nodular sclerosis Hodgkin lymphoma.

through 2017. We reviewed the microscopic descriptions, final diagnoses and comments from all the pathology reports. We selected cases with the diagnosis of CHL in excised lymph nodes with an interfollicular growth pattern or morphologic features suggestive of paracortical, early involvement or focal growth patterns. We also searched for reports describing RS cells, Hodgkin cells or atypical immunoblastic lymphoid cells in interfollicular or paracortical regions. We retrieved the available archived hematoxylin and eosin (H&E) stained slides and the immunohistochemical slides of these cases. We reviewed the slides to confirm the presence of typical RS cells or their Hodgkin cell variants with the appropriate immunoprofiles. In addition, for the well-documented cases of CHL, we searched for any previous lymph node biopsies that were initially diagnosed or described as benign, reactive, negative, and follicular or paracortical hyperplasia. We reviewed the H&E slides of these previous lymph nodes to identify any missed initial diagnosis of CHL with IF involvement. We have included cases of HL with IF involvement that fulfilled the diagnostic criteria of typical RS cells that were positive for CD15 and CD30 and negative for LCA with or without positivity for CD20, EMA and EBV. We have excluded cases that showed atypical large immunoblastic lymphoid cells that were CD15 negative and LCA (CD45RB) positive. We have also excluded cases that showed an effaced nodal architecture, a prominent focal nodule or mass formation of easily recognizable foci of HL and lymph nodes that did not show reactive follicular hyperplasia. We categorized the cases according to the pattern of the nodal architecture, pattern and extent of IF involvement, number of RS cells and the background in the involved IF areas. We looked for any associated lesions or other morphologic variants. We reviewed the IHC slides for each case and categorized the immunoprofile of the RS cells. We studied the following available markers: CD45RB (LCA), CD20, CD79a, ALK, CD3, CD30, CD15, EMA (Epithelial Membrane Antigen) and Epstein Barr virus (EBV) using EBER and EBV-LMP1. We collected the relevant clinical, radiologic and serologic features for each patient. They included the age, gender, initial clinical presentations, levels of erythrocyte sedimentation rate, the site of the excised lymph node, radiologically involved lymph nodes, the stage of the disease, the received treatment; follow up, history of recurrence and survival data. We have tabulated the cases serially according to their chronological order.

3. Results

We found 103 cases of lymph nodes with the diagnosis of CHL. Initially, we found 10 cases that showed features of HL with interfollicular involvement. We have excluded 2 cases that were initially suspected for HL with IF involvement. They did not fulfill the diagnostic criteria of CHL. One case was a 9-year-old boy who had right cervical lymphadenopathy without fever or hepatosplenomegaly. His excised submandibular lymph node showed a characteristic pattern of EBV-associated infectious mononucleosis nodal hyperplasia with atypical large lymphoid cells. These cells were positive for CD30, CD20, LCA and EBV, and were negative for CD15. The patient was well without evidence of lymphadenopathy after 2-years follow up. The other case was a 20-year-old woman that presented with left cervical lymphadenopathy for 3 weeks with fever. Her lymph node showed necrotizing lymphadenitis and focal interfollicular atypical large lymphoid cells. These cells were positive for LCA and CD20 and negative for CD15, CD30, EMA and EBV. The patient was treated with steroids and was well after one year follow up. We identified 8 (7.8%) cases of HLs with a confirmed diagnosis of CHL with an interfollicular growth pattern with typical RS cells and appropriate immunoprofiles (Table 1). The age range was between 3 and 48 years with a mean age of 26 years. The male to female ratio was 7 to 1. Five patients presented with neck swelling without B-symptoms, two with B-symptoms and one with generalized lymphadenopathy and anemia-related dizziness and fatigue. The duration of the clinical presentations ranged from few weeks to 2 months. All of the excised lymph nodes were accessible cervical lymph nodes. Two cases were not staged because one has a missed initial diagnosis and the other one was an outside referral case that has no follow up. The remaining patients presented with stage I and II. Five patients received cycles of chemotherapy with or without localized radiotherapy. One patient did not receive any treatment because the initial diagnosis was benign reactive hyperplasia. Two patients