Article

The Uncommon Faces of Classic Hodgkin Lymphoma

Stefano Fratoni[1,*] and Pasquale Niscola[2]

[1]Department of Surgical Pathology/Hematopathology Section, Saint' Eugenio Hospital, Rome, Italy; [2]Hematology Unit, Saint' Eugenio Hospital, Rome, Italy.

Abstract: Diagnosis of classic Hodgkin lymphoma (CHL) is quite straightforward with the integrated clinical, morphological, and immunophenotypic studies. Due to the variation in morphology and immunophenotype, CHL diagnosis remains a challenge. Based on their many years of experience in diagnostic practice, the authors summarized eleven uncommon variants of CHL: 1) CHL with xanthogranulomatous inflammation, foamy histiocytes and loose granulation tissue-like stroma; 2) epithelioid cell-rich and granulomatous CHL; 3) CHL with prominent keloid-like fibrosis; 4) CHL rich in plump histiocytes arranging in a fascicular pattern; 5) intrasinusoidal CHL; 6) interfollicular CHL: 7) neutrophil-rich CHL; 8) neoplastic cell-rich CHL; 9) lymphocyte depleted CHL; 10) CHL with aberrant immunophenotypes; 11) grey-zone CHL. These variants pose diagnostic pitfalls to the practicing pathologists.

Keywords: Classic Hodgkin lymphoma, anaplastic large cell lymphoma, immunohistochemistry

Introduction

The diagnosis of Hodgkin lymphoma in the modern era relies on an appropriate clinical setting, morphological and immunophenotypic assessment. The 2016 WHO Classification of Hematopoietic and Lymphoid Neoplasms [1] recognizes two biologically distinct entities regarding Hodgkin Lymphoma: classic Hodgkin lymphoma (CHL) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). Furthermore, CHL is further divided into four subtypes: nodular sclerosis classical Hodgkin lymphoma (NSCHL), mixed cellularity classic Hodgkin lymphoma (MCCHL), lymphocyte rich classic Hodgkin lymphoma (LRCHL) and lymphocyte depleted classic Hodgkin lymphoma (LD-CHL) [1]. The typical histologic pattern of these entities had been largely described by the literature and consolidated by the daily experience of the clinical pathologist as well. Then, either academic and practical hematopathologists as well as surgical pathologists are quite confident with their recognition under the microscope.

Moreover, CHL occasionally may show some uncommon histologic pattern of growth rendering their diagnosis difficult, opening several issues around their challenging differential diagnosis. This review briefly describes some challenging cases of CHL with uncommon histopathologic features we have encountered during our daily practice. As a matter of fact, the authors report their own experience on diagnostic pitfalls and conditions which mimic CHL.

[*]Correspondence: Stefano Fratoni, Department of Surgical-Pathology, S. Eugenio Hospital, Piazzale dell'Umanesimo n° 10, 00144, Rome, Italy. Tel: +390651002875; Fax: +39065102875; E-mail: stefano.fratoni@aslroma2.it

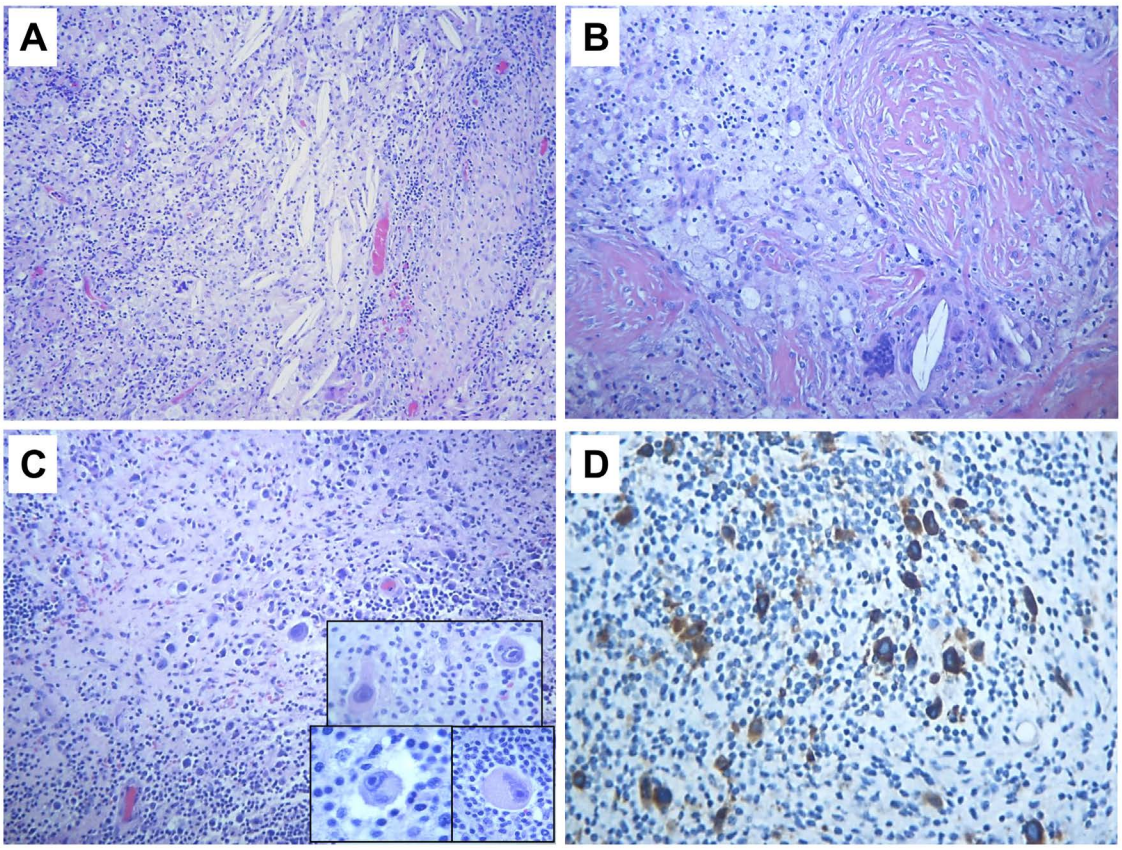

Figure 1: Classic Hodgkin lymphoma with xanthogranulomatous inflammation, foamy histiocytes and loose granulation tissue-like stroma. A, Prominent xanthogranulomatous features are present admixed with foamy histiocytes and fibrotic stroma (H&E, x10). B, Edema and granulation tissue inflammatory-like stroma are also present (H&E, x20); C, scattered neoplastic HRS cells are detected inside this peculiar inflammatory milieu (H&E, x40). D, CD30 immunostain highlights neoplastic cells (Immunoperoxidase, x40) while CD3 immunostain shows prominent rosettes around HRS cells (not shown).

Classical Hodgkin lymphoma with xanthogranulomatous inflammation, foamy histiocytes and loose granulation tissue-like stroma

Variakojis D. *et al* in 1972 described the presence of foamy macrophages in Hodgkin lymphoma [2]. Nevertheless, very rare cases of CHL may have a prominent xanthogranulomatous inflammatory reaction with a lot of foamy histiocytes embedded into a loose edematous granulation-tissue-like stroma (Figure 1). Neoplastic Hodgkin-Reed-Sternberg (HRS) cells are quite scanty and express the typical CHL phenotype: CD30+/CD15+/-/PAX5+/IRF4/MUM1+/CD45(LCA)-/CD20-/CD3-/CD68(RPGM1)-. EBV infection evaluated by in situ hybridization for EBV encoded RNA (EBER) may be present or absent. This rare pattern in CHL produces a challenging diagnosis with xanthogranulomatous lymphadenopathy. Careful histologic examination and immunohistochemical work-up are mandatory for correct diagnosis.

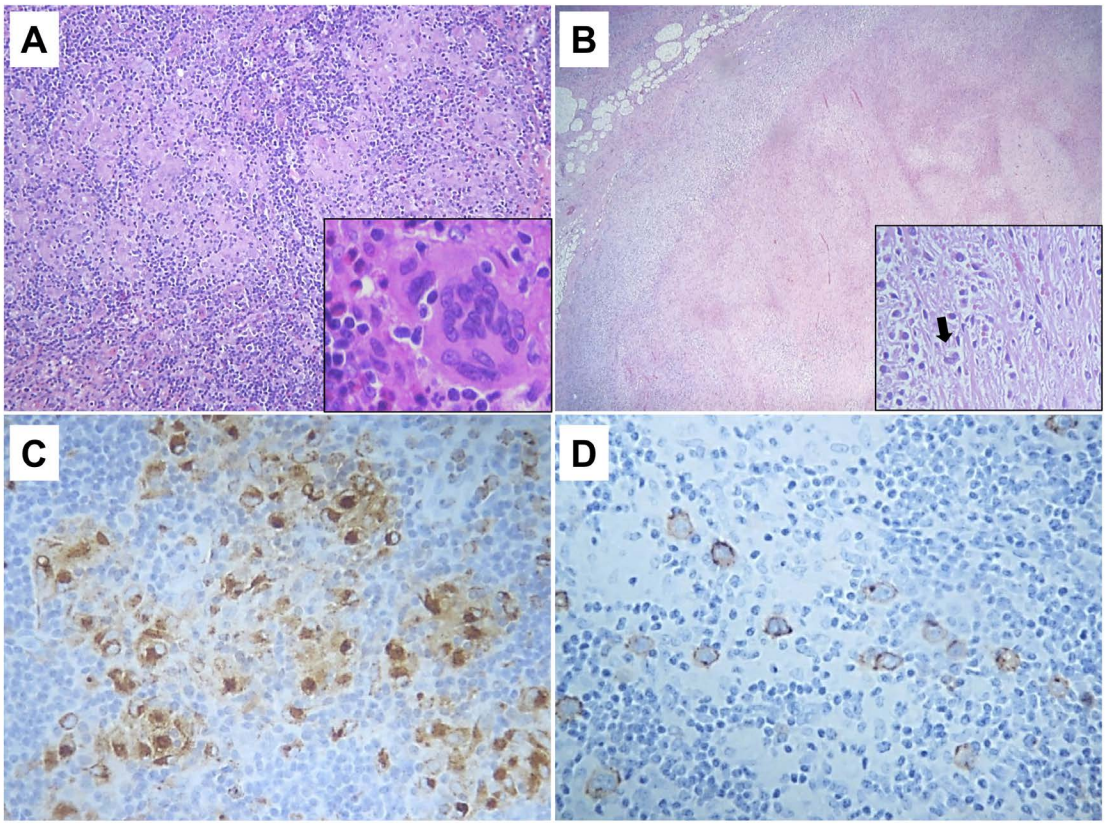

Figure 2: Classic Hodgkin lymphoma with epithelioid granulomas and coagulative necrosis. A, CHL with microgranulomata composed of epithelioid histiocytes (H&E, x200). Rare multinucleated giant cells are also present (inset); B, CHL with prominent coagulative necrosis; HRS cells located at the edge of necrosis (inset); C, Microgranulomata revealed by CD68PGM1 immunostain (Immunoperoxidase, x40); D, CD30+ Hodgkin lymphoma cells (Immunoperoxidase, x400) in the granulomatous background.

Epithelioid cell-rich and granulomatous classic Hodgkin Lymphoma

CHL has long been notorious for granulomatous appearance [3]. Moreover, on rare cases a prominent epithelioid cell reaction (granulomatous reaction) may obscure the neoplastic cells, which makes the diagnosis more challenging. The histiocytes may be arranged in three patterns: 1) coalescing small clusters of scattered epithelioid histiocytes representing a background of microgranulomata; 2) well-formed non-necrotizing (sarcoid-like) granulomas (Figure 2 A); and 3) necrotizing granulomas with peripheral palisading histiocytes around large central foci of coagulative neoplastic necrosis (Figure 2B).

In this setting, lymphoma cells are often detected at times after a laborious search. Florid proliferation of histiocytes in the milieu of CHL leads first to the differential diagnosis of granulomatous disease. Our best diagnostic weapon is a high degree of suspicion. In nodal granulomatous lesions, careful examination for atypical cells located between the microgranulomata and/or lining the areas of necrosis is mandatory; if you have any doubts perform immunohistochemistry: CD30 as first screen is quite useful. HRS cells typically form large clusters or sheets at the edge of necrosis. We usually screen any case of granulomatous lymphadenopathy with

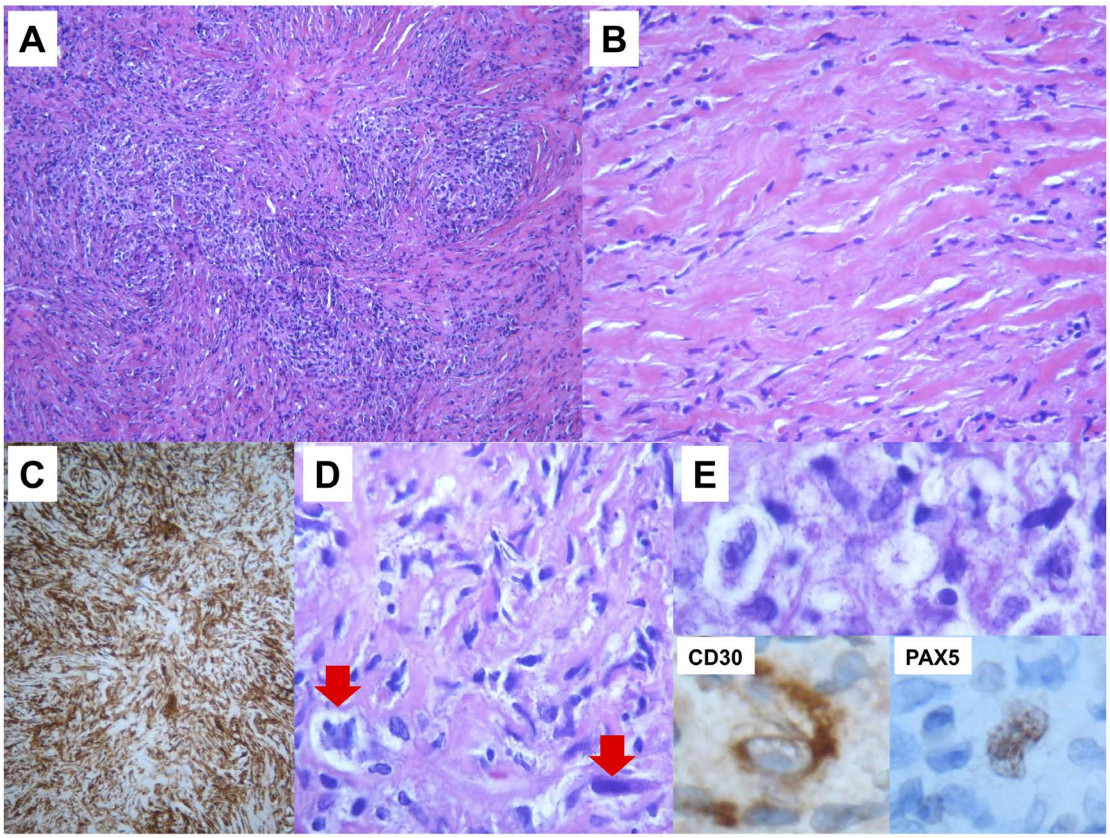

Figure 3: Classic Hodgkin lymphoma with prominent keloid-like fibrosis. A, A fibrotic lesion with storiform pattern of growth (H&E, x40); B, A striking collagenized stroma like a scar or keloid (H&E, x200); histiocyte-rich background is revealed by CD163 immunostain (C). D, Inside the fibrohistiocytic stroma, scattered atypical large cells are detected after a laborious search (indicated by red arrows) and HRS cells entrapped in the fibrotic stroma may appear as atypical spindle-shaped cells; E, Rare typical lacunar HRS cells were also present as revealed by immunostain for CD30 (inset) and PAX5 (inset).

CD30 immunostain, looking for large atypical HRS cells, excluding activated immunoblasts and plasma cells. The surgical pathologists should be aware that histiocytes may be CD15+ but they are CD30- and CD68(KP1)+/CD68(RPGM1)+/CD163+.

Classic Hodgkin lymphoma with prominent keloid-like fibrosis

Rare cases of CHL (usually in the NSCHL category) can show a background of many fibroblasts admixed with numerous histiocytes. Delicate interstitial fibrosis is quite easy to find but rarely the collagen fibers may be coarse, large and strongly eosinophilic, displaying a keloid-like reaction. On low power examination this fibroblastic-histiocytic pattern may have a spindle and storiform configuration reminiscent of a mesenchymal proliferation. Furthermore, few neoplastic cells are embedded in the fibrotic stroma (Figure 3). Pathologists should be aware that the HRS cells can assume a spindle configuration as a result of passive entrapment into the fibrotic stroma. From a diagnostic point of view these changes may represent a diagnostic pitfall. Our approach for

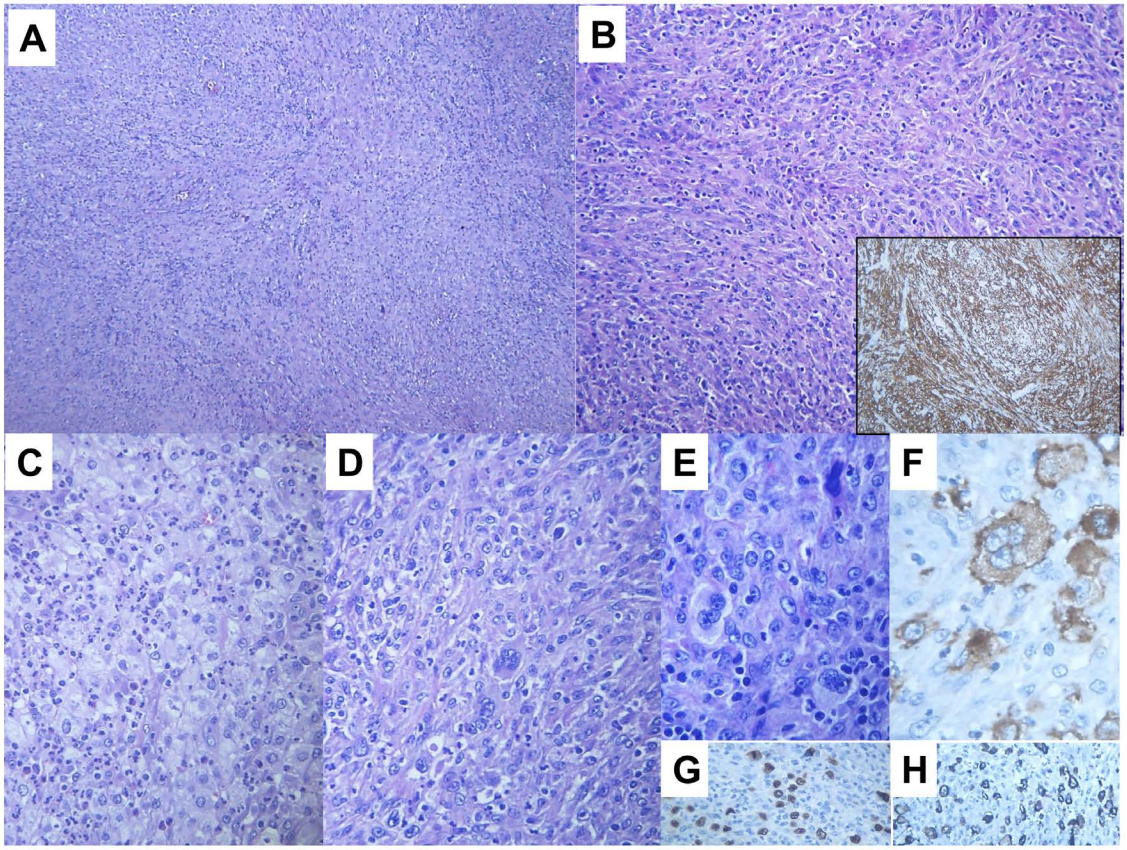

Figure 4: Classic Hodgkin lymphoma rich in plump histiocytes arranged in a fascicular pattern. A, Low magnification show a tumor with a striking storiform pattern of growth; B, The fascicular pattern is well illustrated where medium sized spindle histiocytes are prevalent as showed by CD163 immunostain (inset); C, The "reactive" background shows clusters of foamy histiocytes and neutrophils; D & E. Scattered pleomorphic HRS cells (H&E, x200) are positive for CD30 (F), PAX5 (G) and EBV-LMP1 (H). Other B-cell markers (CD20 and CD79a) were not expressed (data not shown).

any mediastinal fibroblastic-like lesion with a storiform pattern is a careful search for atypical cells on medium power, followed by a work-up including CD30 immunostain.

Classic Hodgkin lymphoma rich in plump histiocytes arranging in a fascicular pattern

Rare cases of CHL (usually also in the NSCHL category) reveal a background composed of a "sea" of spindly and plump histiocytes with abundant amphophilic cytoplasm, arranging in a prominent fascicular pattern of growth. Large atypical neoplastic cells are scattered between the histiocytes (Figure 4). This pattern may pose a diagnostic challenge and mimics several non-neoplastic and neoplastic lesions with a fascicular pattern of growth, such as nodal inflammatory pseudotumor, nodal palisading myofibroblastoma, metastatic spindle cell carcinoma/melanoma, Kaposi sarcoma, spindle cell subtype of diffuse large B-cell lymphoma (DLBCL), and sarcomatoid anaplastic large cell lymphoma (ALCL).

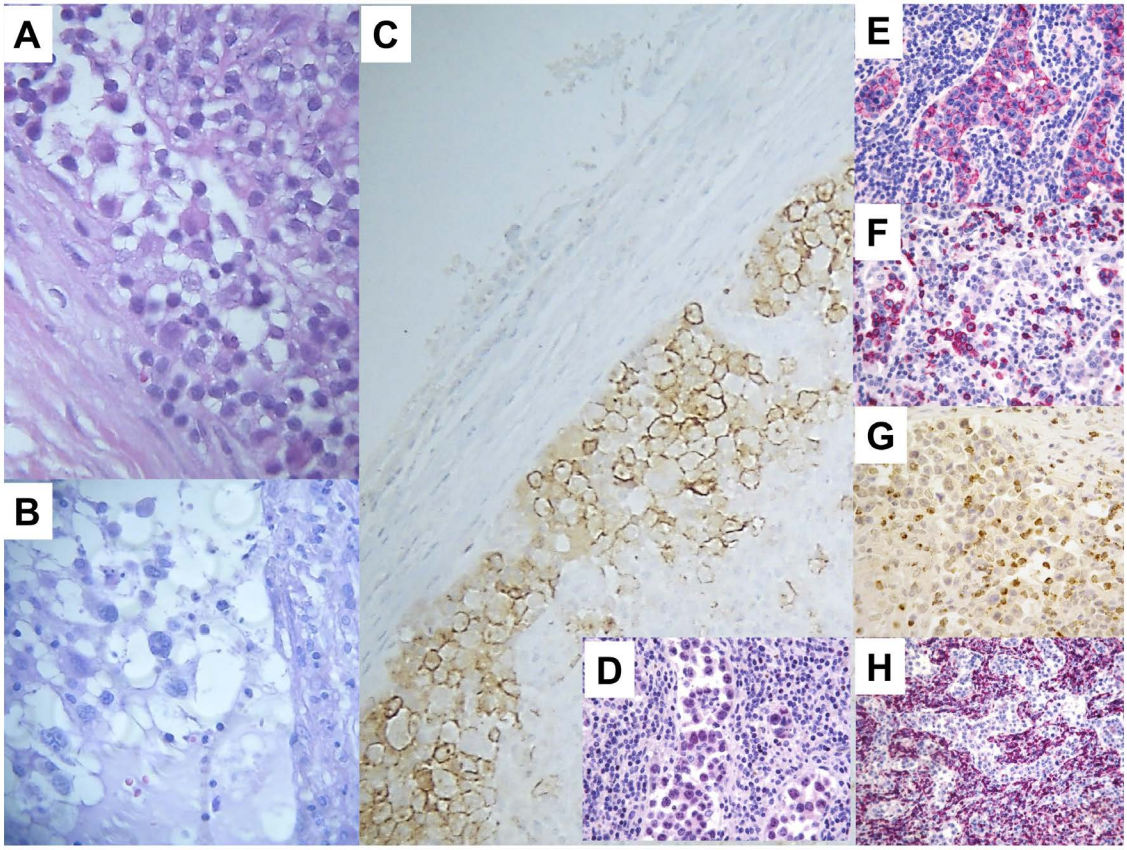

Figure 5: Nodular sclerosis classic Hodgkin lymphoma with unusual intrasinusoidal pattern of infiltration. A & B, The neoplastic cells are located within the subcortical sinus (H&E, x200). Unequivocal expression of CD30 (C), PAX5 (D), CD15 (E) and CD79a (F) confirms Hodgkin Lymphoma. Granzyme B (G) and CD43 (H) were absent [with permission of Professor Stefano Ascani MD, Perugia School of Medicine University of Perugia, Italy]

The differential also includes the accessory cell malignant neoplasms, such as histiocytic sarcoma, follicular dendritic cell sarcoma, interdigitating dendritic cell sarcoma, and Langerhans cell sarcoma. EBV-positive DLBCL polymorphic variant could be suspected in the case illustrated here, but CD45 and the B-cell markers such as CD79a and CD20 were negative in the neoplastic cells. Our approach for any nodal lesion with a prominent fascicular pattern is a search for atypical cells on medium/high power followed by a careful workup always including immunostains for CD30, B-cell markers, CD15, EBV(LMP1), EBV encoded RNA(EBER), ALK or ALKp80, dendritic-cell markers, CD163, CD117, CD31, CD34, HHV8, S100 and AE1/AE3.

Intrasinusoidal classic Hodgkin lymphoma

Occasionally, in some cases of CHL, HRS cells are peripherally located in the sub-capsular region of the lymph node around sinus. In this setting it is possible to find neoplastic cells mainly situated within sinusoidal spaces (Figure 5). They show unequivocal expression of CD30/CD15/PAX5/OCT2 and rarely CD79a and CD20 with no expression of Bob1 and without aberrant expression to suggest anaplastic

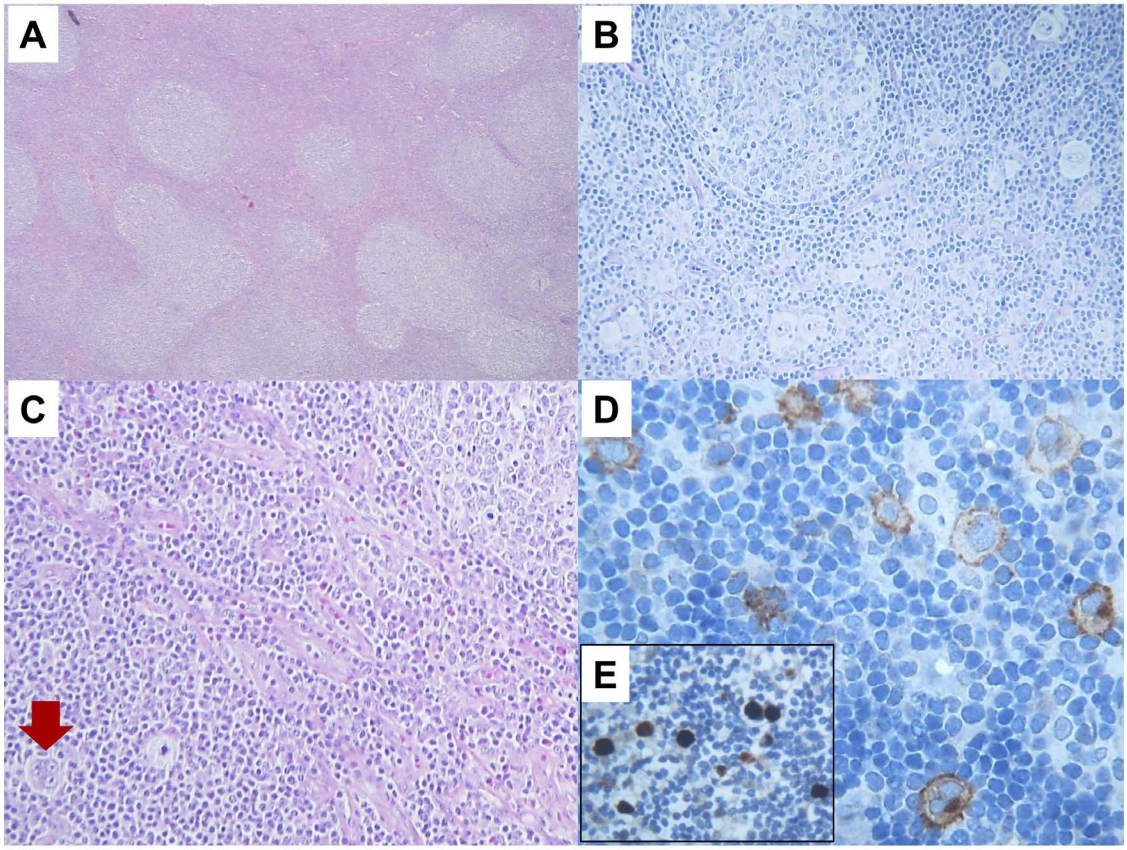

Figure 6: Interfollicular classic Hodgkin lymphoma. A, Low magnification show prominent follicular hyperplasia (H&E, x40); B & C, Medium magnification reveals rare scattered HRS cells in the interfollicular region (H&E, x100); D, CD30 immunostain reveals neoplastic cells with typical paranuclear Golgi pattern of expression. E, Positive EBV encoded RNA (EBER).

large cell lymphoma (ALCL): EMA-/LCA-/CD43-/CD2-/CD3-/CD4-/CD5-/CD7-/CD8-/CD56-/UCHL1-/ALKp80-/ALK1/CD246-/BCL6-/TIA1-/GranzymeB-/perforin-. EBV expression may be positive or negative. Furthermore, T-Cell Receptor gene rearrangement is absent and FISH for *DUSP22* and *TP63* should be negative.

This rare case suggests that although cases of CHL with an intrasinusoidal pattern are very rare, nevertheless do exist. However, a striking intrasinusoidal invasion by CD30+ neoplastic cells is typically seen in ALCL, then this exceptional finding in CHL mimicking ALCL very likely leads to a mistaken diagnosis of ALCL. Hematopathologists must be aware that a wide panel of antibodies should be used to confirm the diagnosis of CHL with uncommon intrasinusoidal pattern of infiltration [4].

Interfollicular classic Hodgkin lymphoma

In some cases of CHL the HRS cells may be predominantly located in the interfollicular region. In this scenario the surrounding florid follicular hyperplasia may be prominent and can mask the scattered HRS cells. These may be identified at the edge, outside or directly adjacent to the reactive follicles or

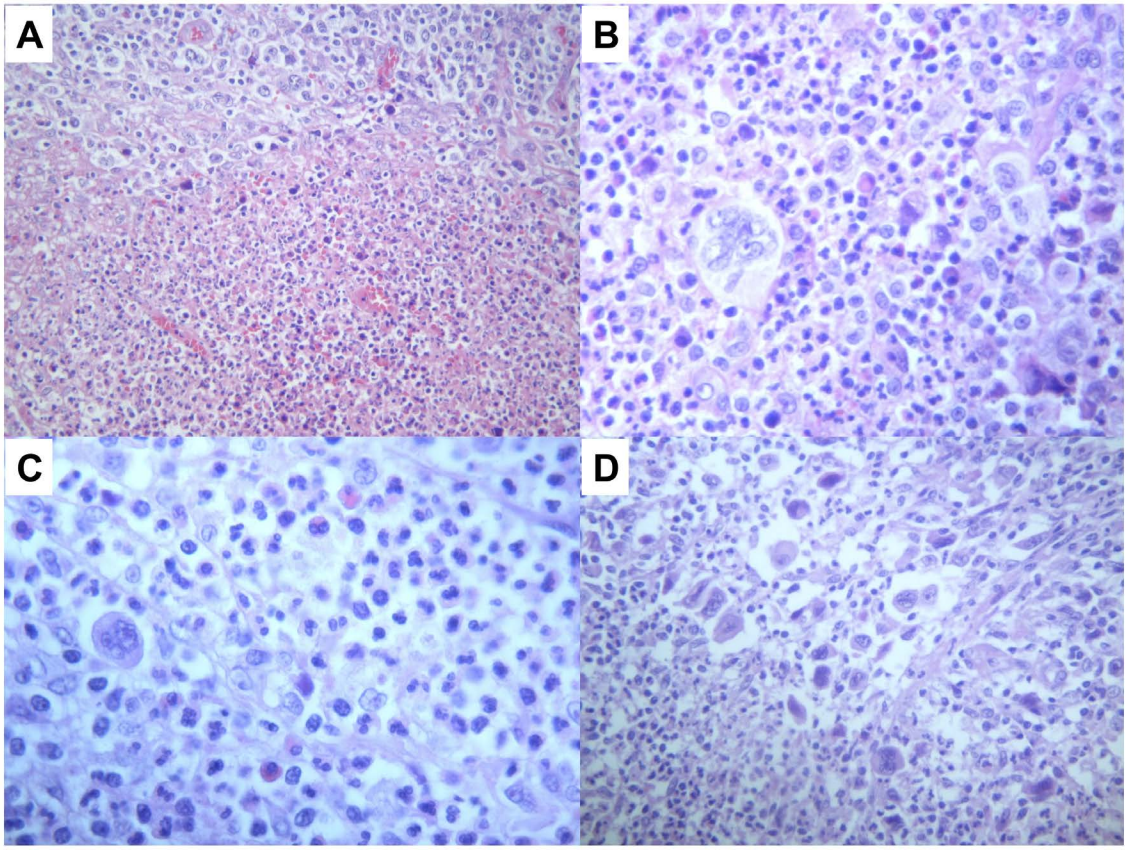

Figure 7: Neutrophil-rich classic Hodgkin lymphoma. A, HRS cells located at the edge of a large focus of suppurative necrosis (H&E, x200); B & C, Rare pleomorphic HRS cells embedded in a neutrophil-rich background (H&E, x400); D, Small clusters of neoplastic cells may occasionally be detected (H&E, x200).

may involve interfollicular areas between reactive follicles: this represents the so called "interfollicular Hodgkin lymphoma" (Figure 6).

Lymphoid follicles usually show hyperplastic germinal centers but occasionally they may show involuted and atrophic changes resembling those seen in hyaline-vascular Castleman disease. Such cases usually cannot be subclassified. Interfollicular Hodgkin lymphoma probably represents an early or partial lymph node involvement by CHL, MC or NS subtype.

There is possible diagnostic confusion with the so called "interfollicular Hodgkinoid lymphadenitis" [5], a reactive lymphadenopathy showing interfollicular proliferation of activated immunoblasts which may mimic HRS cells. These cells show a variable expression of CD30 (from weak to strong), but CD15 is usually negative. In this setting lymphadenopathy related to viral infections, autoimmune diseases and drug-induced hypersensitivity reactions may produce examples of lymphadenitis with "interfollicular hodgkinoid" background. Scrutiny of the interfollicular areas in any cases of unexplained florid follicular and paracortical hyperplasia is indicated. In addition, a large panel of phenotypic work-up including CD30, CD15 and EBER should be performed in any cases of otherwise unexplained lymphadenopathy with prominent reactive changes. Furthermore, clinical correlation is imperative.

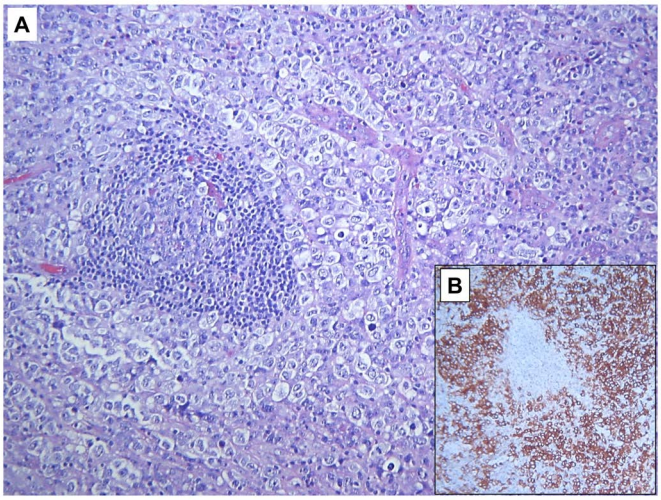

Figure 8: Neoplastic cell-rich classic Hodgkin lymphoma. A, Sheets of large atypical neoplastic cells with pleomorphic morphology surround a remnant lymphoid follicle (H&E, x200); B, Immunostain reveals that these cells are CD30+ (x100). PAX5, IRF4/MUM1 and CD15 were also expressed, while CD20, CD43, ALK1, EMA as well as T-cell antigens were absent (data not shown).

Neutrophil-rich classic Hodgkin lymphoma

In some cases of nodular sclerosis CHL the center of the nodules may show extensive suppurated necrosis [neutrophil-rich necrosis], then scattered HRS cells may be obscured by the number of neutrophils, leading to an erroneous diagnosis of suppurated lymphadenitis, likewise cat-scratch disease (Figure 7). Best place to search for HRS cells is around the necrotic foci. In fact, HRS cells typically form large clusters or sheets at the edge of necrosis. CD30 immunostaining will highlight the neoplastic cells.

Neoplastic cell-rich classic Hodgkin lymphoma

Occasionally, rare cases of classic Hodgkin lymphoma are composed of a great number of neoplastic cells forming cohesive aggregates and sheets (Figure 8). The HRS cells often lack the typical lacunar or Reed-Sternberg cell features but may show bizarre appearance resembling immunoblasts, likewise a large cell non-Hodgkin lymphoma, ALCL, germ cell tumor, carcinoma, epithelioid-sarcoma, and melanoma. Careful immunohistochemical workup is often required to reveal the nature of HRS cells.

Lymphocyte depleted classic Hodgkin lymphoma

Lymphocyte depletion variant of classic Hodgkin lymphoma (LDCHL) is now considered a neglected entity. This rare subtype of CHL is often associated with an aggressive clinical course, widespread involvement including bone marrow at diagnosis and more common B symptoms [6]. The cellular composition is represented by a great abundance of histiocytes and a lot of pleomorphic HRS cells (also known as "sarcomatous" Hodgkin lymphoma). EBV-encoded RNA EBER is positive in 80% of LDCHL (Figure 9).

Aberrant immunophenotypic finding in classic Hodgkin lymphoma

The classical phenotype of HRS cells is well known to pathologists all around the world. Nevertheless, Hodgkin lymphoma cells may show aberrant or unusual phenotypic findings as well. Illustrated here (Figure 10) is a neoplastic cell-rich CHL with aberrant expression of CD4, Perforin, EMA and cytokeratin AE1/AE3. T-cell receptor gene rearrangement was not detected in this case.

Typical HRS cells are usually negative for B-cell markers such as CD22, CD79a, CD19 and CD20, but one of these antigens may be expressed in about 20% of the CHL cases [7]. Sporadically, diffuse and bright CD20 membranous staining may occur in some CHL cases. Thus, bright CD20 expression does not exclude CHL if other clinicopathologic and

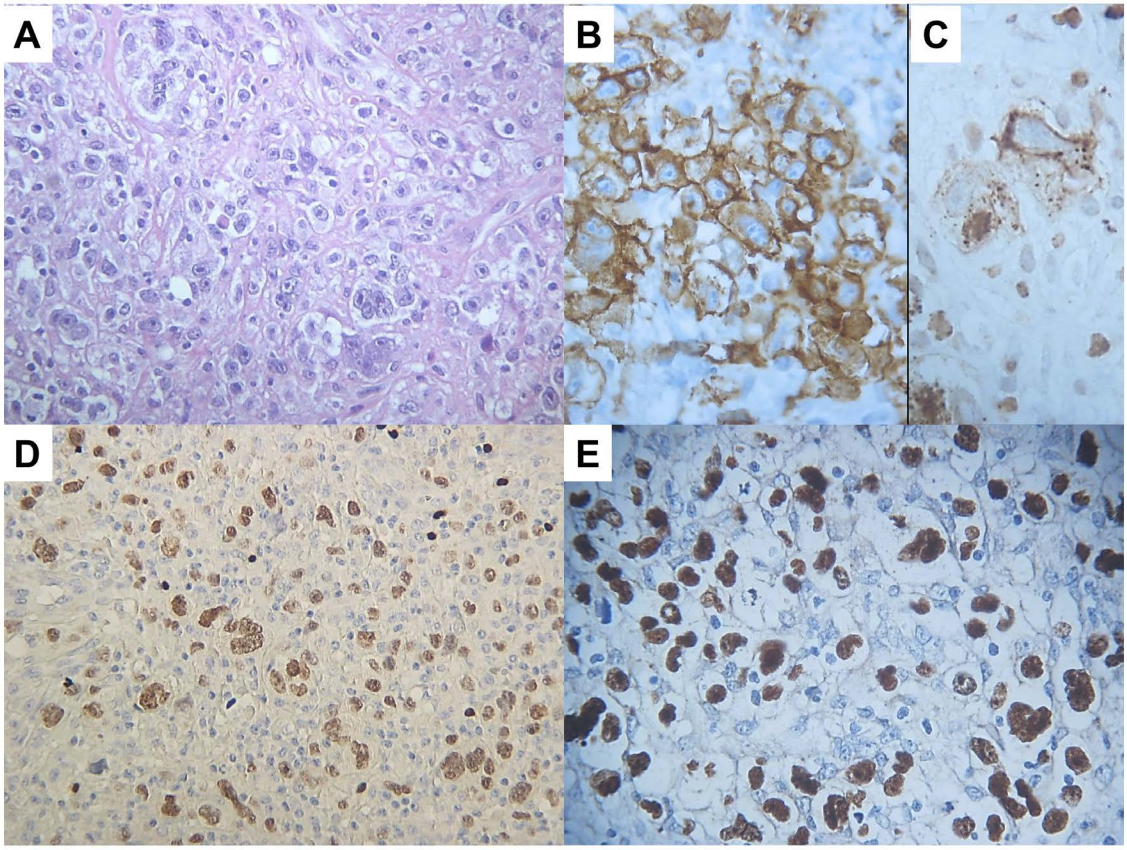

Figure 9: Lymphocyte-depleted classic Hodgkin lymphoma. A, Medium magnification reveals sheets of pleomorphic bizarre and/or multinucleated HRS cells (H&E, x200). Immunostains for CD30 (B), CD15 (C) and PAX5 (D) reveal the typical phenotype of classic Hodgkin lymphoma. E, EBV encoded RNA (EBER) is strongly positive.

phenotypic findings fit with CHL. On the other hand, strong positivity for CD20 in a neoplasm otherwise compatible with CHL should not lead to classifying the tumor as a lymphoma with features intermediate between classic Hodgkin lymphoma and DLBCL (grey zone lymphomas).

Furthermore, peripheral T-cell lymphoma and ALCL infrequently express CD15 and very rarely express PAX5 as well, including ALK-negative ALCL [8–12]. Aberrant expression of PAX5 in ALCL is around 3% [13]. Epithelial membrane antigen (EMA) is usually not expressed in Hodgkin lymphoma, but based on my personal observation, EMA can be positive in certain neoplastic cells in some cases of CHL.

Although dendritic cell markers such as clusterin and fascin may be expressed by HRS cells, expression of other antigens such as D2-40/CD35/CD21 is nearly absent in all studied cases [15], although occasional expression of CD23 may be detected on HRS cells [16, 17]. Finally, expression of cytokeratin by HRS cells is an exceptional and rare phenomenon [18]; I have seen only two sporadic CHLs which expressed pancytokeratin AE1/AE3 with a "dot-like" pattern.

The T-cell antigen CD43 is usually absent in CHL. A diffuse and strong expression of CD43 in an ALK-negative large cell tumor with "Hodgkin-like" features should promptly suggest the possibility of an ALK-negative ALCL. Cytotoxic molecules such as

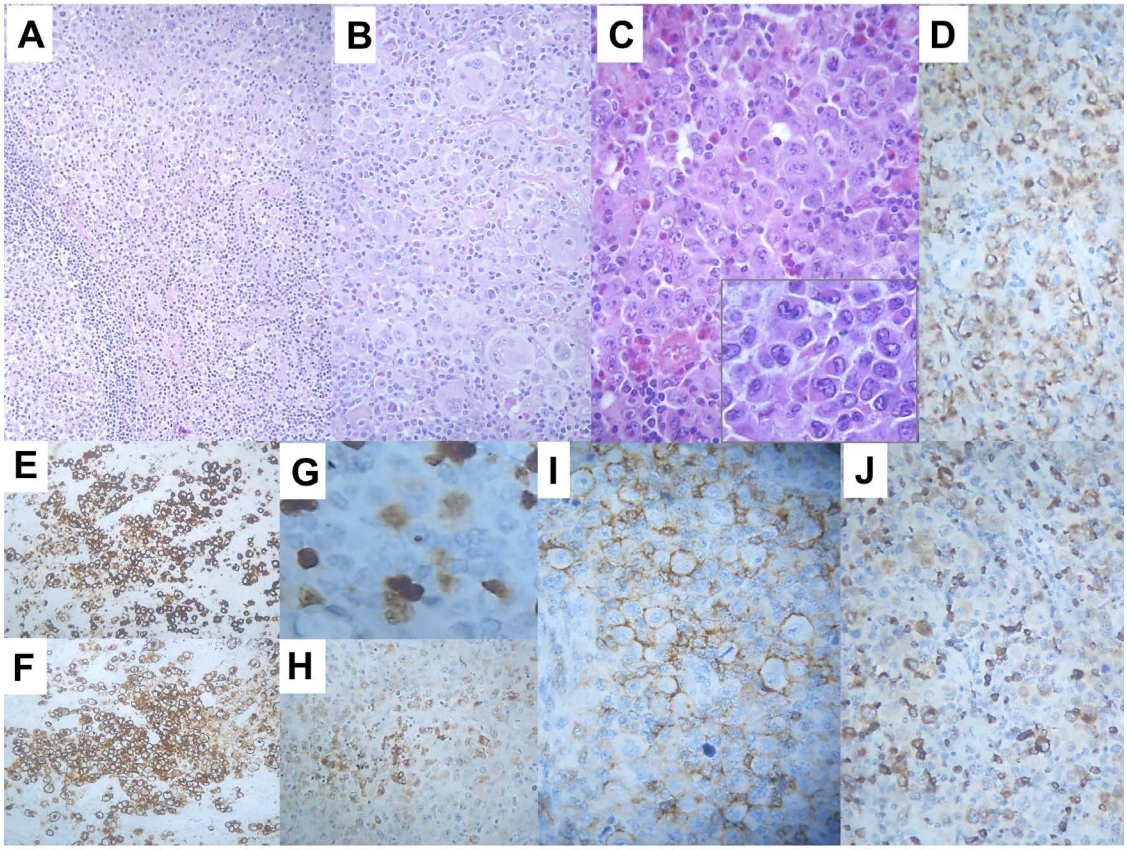

Figure 10: Neoplastic cell-rich CHL with aberrant phenotype mimicking ALK-negative ALCL. A, Medium magnification shows perifollicular large sheets of large pleomorphic cells (H&E, x100); some clusters of tumor cells show prominent multinucleation (B) and hallmark cell-like morphology (C) (H&E, x400); D, perinuclear expression of cytokeratin AE1/AE3 in the majority of the tumor cells; E, positive for CD15; F, positive for CD30; G, positive for PAX5; H, positive for EMA; I & J, Aberrant expression of T-cell markers CD4 and perforin was also detected in a subset of neoplastic cells.

perforin, granzyme B and TIA1 are expressed by HRS cells in 10-20% of the cases [8]; in addiction, HRS cells may also express one or more T-cell markers in 10-15% of the CHL cases; they are more often CD2, CD3, CD4, and CD7. In these cases, expression of the T markers is aberrant and a clear-cut relationship with the outcome of the disease is suspected [9]. Routine testing of a T-cell antigen panel (at least CD3, CD2 and CD4) in CHL could be recommended because this testing may indicate those patients have a poor prognosis.

Nevertheless, these CHLs with aberrant T-cell antigen expression often have some histological features of ALCL: numerous tumor cells, high cohesiveness, more pleomorphism with a horseshoe-shaped nucleus, sinusoidal infiltrating pattern, multiple tumor necrosis and occasionally PAX5 negativity [12]. Vice versa, rare ALCL cases show "Hodgkin-like" features such as a prominent nodular-sclerosis pattern of growth as well as tumor cells with striking "Hodgkin-Reed-Sternberg" morphology.

Therefore, a careful immunohistochemical and molecular work-up should be performed to avoid a misdiagnosis because CHL and ALK-negative ALCL

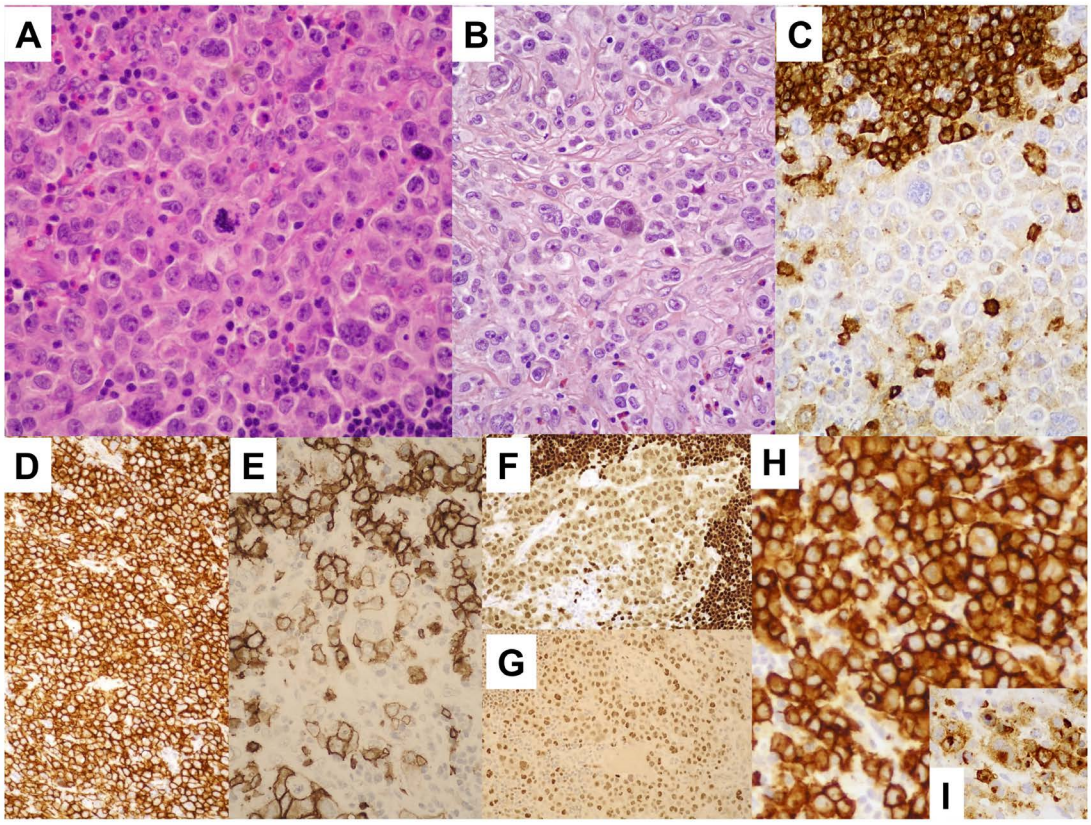

Figure 11: Grey zone lymphoma. A & B, This lymphoma is composed of large immunoblast-like cells admixed with pleomorphic cells with multilobated nuclei and striking Hodgkin-like morphology; background eosinophils are present (H&E, x200); C, CD45RB (LCA) was absent on tumor cells; D, heterogeneous CD20 expression: some areas showing a strong and diffuse while other areas showing expression only in a minority of the tumor cells; E, Hodgkin-like cells were CD20 negative. Expression of transcription factors PAX5 (F), OCT2 (G), CD30 (H), CD15 (I). CD79a, BCL6, IRF4/MUM1 were also expressed by the tumor cells (data not shown) [with permission of Professor Stefano Ascani MD, Perugia School of Medicine University of Perugia, Italy]

have distinct prognosis and treatment options; CHL can be cured with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) therapy in more than 80% of patients [19, 20], whereas ALK-negative ALCL often shows poor outcome and requires a different type of treatment. Because of this it is very important to distinguish these two entities.

In conclusion, classic Hodgkin lymphoma and ALK-negative ALCL share many morphological and immunohistochemical features, causing difficulties in making diagnosis. A better genetic definition of the CHL with aberrant expression of T-cell antigens and ALK-negative ALCL will allow us to identify aberrant genes differentially expressed in CHL and ALCL to improve our comprehension of pathways altered in these two diseases. Whole exome sequencing (WES) of these cases with aberrant gene expression revealed similar genetic features between CHL and ALCL. The genetic findings show that when HRS cells aberrantly expressed T-cell antigen(s), they seemed to lose some of their CHL features and gain some ALCL features. On the other hand, when ALCL cells aberrantly expressed B-cell antigen(s), they also lost some of the ALCL features and ac-

quired some of the CHL features. This outcome is consistent with the morphological findings [12].

Grey-zone lymphomas

Illustrated in this paragraph is a rare example of malignant lymphoma with morphologic features suggestive of either CHL or DLBCL with HRS-like cells. It has a discordant immunophenotype between CHL and DLBCL (Figure 11). The concept of grey zone lymphomas encompasses a B-cell lineage lymphoma with overlapping morphologic and phenotypic findings between primary mediastinal large B-cell lymphoma (PMLBCL) and nodular sclerosis CHL. This was confirmed by gene expression profiling analysis that revealed an overlapping molecular signature between nodular sclerosis CHL and PMLBCL [21, 22]. In our opinion, this issue does not constitute one biologic entity but rather represents a pool of rare single cases that exhibit a phenotype with transitional findings between CHL and DLBCL [23]. Currently, there are no uniform diagnostic criteria by which these lymphomas should be classified. These lymphomas usually occur in the mediastinum, thus called mediastinal grey zone lymphomas (MGZL), but peripheral lymph nodes may be primarily involved as well [24]. These lymphomas are composed of confluent sheets of pleomorphic cells, resembling centroblasts and/or lacunar/HRS-like cells, encompassing a broad spectrum of cytological morphology. Discordance between cytological features and immunohistochemical findings represents the key feature of this type of tumors [25]. Furthermore, EBV expression has been reported in 15% of the cases by EBER [1].

Practically, these tumors are cell-rich neoplasm where neoplastic cells have centroblastic or immunoblastic morphology, not infrequently with pleomorphic Hodgkin-like features, sometimes with true binucleate HRS-like cells. Morphologically, it is quite difficult or impossible to differentiate a cell-rich CHL from a PMLBCL. Thus, immunohistochemistry (IHC) is helpful to make this differential easy in routine practice. If the IHC results are inconclusive, aberrant or conflicting for either CHL or PMLBCL, we likely have a grey-zone lymphoma. We believe in this setting that a diagnosis of grey-zone lymphomas may be right.

Rarely, cases of composite DLBCL and CHL in the same lymph node as well as in sequential tumors may also occur. These lymphomas are related to the special entity of grey zone lymphomas and lineage plasticity likely explains for the transition between CHL and DLBCL and vice versa. Due to the tumor heterogeneity in different areas of a neoplasm, practicing pathologists, hematopathologists, and clinicians should be aware that making diagnosis from core-needle biopsied specimens is not recommended. Moreover, diagnosis of grey zone lymphoma has important clinical indication as it has been recommended that these patients be treated with dose-intensive regimens [26, 27].

Conclusions

This brief review reminds us that classic Hodgkin lymphoma may occasionally acquire uncommon histopathologic and immunophenotypic features and a variety of lymphoid proliferations may resemble classic Hodgkin lymphoma. This article emphasizes the importance of a careful clinical history and an adequate surgical excisional biopsy for proper diagnosis. In challenging cases, appropriate immunophenotypic and molecular studies are mandatory to obtain the correct diagnosis. The initial diagnosis should be made on an adequate tissue biopsy. A fine needle aspiration or even a needle core biopsy is inadequate, as the assessment of architecture is important for an accurate diagnosis. Expert consultation should be performed as a tool for good medical practice in difficult cases. Furthermore, right communication between the treating clinicians and the surgical pathologist/hematopathologist is critical for establishing an initial diagnosis as well as for patient management.

Acknowledgements

The authors wish to thank Professor Stefano Ascani MD, Perugia School of Medicine University of Perugia, Italy, for contributing figures 5 and 11. The authors wish to thank Mrs. Laura Borrelli of Department of Surgical Pathology S. Eugenio Hospital of Rome for slides preparation and immunohistochemistry.
The authors have declared that no competing interests exist.
Received: November 26, 2018 **Accepted**: August 12, 2019
Published: November 20, 2019

References

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016; 127: 2375-2390.
2. Variakojis D, Strum SB, Rappaport H. The foamy macrophages in Hodgkin's disease. Arch Pathol. 1972; 93: 453-456.
3. Patsouris E, Noël H, Lennert K. Cytohistologic and immunohistochemical findings in Hodgkin's disease, mixed cellularity type, with a high content of epithelioid cells. Am J Surg Pathol. 1989; 13: 1014-1022.
4. Lee SS, Ryoo BY, Park YH, et al. Hodgkin lymphoma with unusual intrasinusoidal pattern of infiltration. Leuk Lymphoma. 2004; 45: 2135-2141.
5. Fellbaum C, Hansmann ML, Lennert K. Lymphadenitis mimicking Hodgkin's disease. Histopathology. 1988; 12: 253-262.
6. Klimm B, Franklin J, Stein H, et al. Lymphocyte-depleted classical Hodgkin's lymphoma: a comprehensive analysis from the German Hodgkin study group. J Clin Oncol. 2011; 29: 3914-3920.
7. Schwering I, Bräuninger A, Klein U, et al. Loss of the B-lineage-specific gene expression program in Hodgkin and Reed-Sternberg cells of Hodgkin lymphoma. Blood. 2003; 101: 1505-1512.
8. Asano N, Oshiro A, Matsuo K, et al. Prognostic significance of T-cell or cytotoxic molecules phenotype in classical Hodgkin's lymphoma: a clinicopathologic study. J Clin Oncol. 2006; 24: 4626-4633.
9. Venkataraman G, Song JY, Tzankov A, et al. Aberrant T-cell antigen expression in classical Hodgkin lymphoma is associated with decreased event-free survival and overall survival. Blood. 2013; 121: 1795-1804.
10. Gorczyca W, Tsang P, Liu Z, Wu CD, et al. CD30-positive T-cell lymphomas co-expressing CD15: an immunohistochemical analysis. Int J Oncol. 2003; 22: 319-324.
11. Pletneva MA, Smith LB. Anaplastic large cell lymphoma: features presenting diagnostic challenges. Arch Pathol Lab Med. 2014; 138: 1290-1294.
12. Liang K, Wang J, Wang Y, et al. The histological, immunohistochemical and genetic features of classical Hodgkin lymphoma and anaplastic large cell lymphoma with aberrant T-cell/B-cell antigen expression. Hum Pathol. 2019; 84: 309-320.
13. Feldman AL, Law ME, Inwards DJ, Dogan A, McClure RF, Macon WR. PAX5-positive T-cell anaplastic large cell lymphomas associated with extra copies of the PAX5 gene locus. Mod Pathol. 2010; 23: 593-602.
14. Arun I, Roy P, Arora N, Bhave SJ, Nair R, Chandy M. PAX-5 Positivity in Anaplastic Lymphoma Kinase-Negative Anaplastic Large Cell Lymphoma: A Case Report and Review of Literature. Int J Surg Pathol. 2017; 25: 333-338.
15. Kim SH, Choe JY, Jeon Y, et al. Frequent expression of follicular dendritic cell markers in Hodgkin lymphoma and anaplastic large cell lymphoma. J Clin Pathol. 2013; 66: 589-596.
16. Sandvej KB, Hamilton-Dutoit SJ, Pallesen G. Influence of Epstein-Barr virus encoded latent membrane protein 1 on the expression of CD23 antigen, ICAM-1 and LFA-3 in Hodgkin and Reed-Sternberg cells. A morphometric analysis. Leuk Lymphoma. 1993; 9: 95-101.
17. Armstrong AA, Gallagher A, Krajewski AS, et al. The expression of the EBV latent membrane protein (LMP-1) is independent of CD23 and bcl-2 in Reed-Sternberg cells in Hodgkin's disease. Histopathology. 1992; 21: 72-73.
18. Adams H, Schmid P, Dirnhofer S, Tzankov A. Cytokeratin expression in hematological neoplasms: a tissue microarray study on 866 lymphoma and leukemia cases. Pathol Res Pract. 2008; 204: 569-573.
19. Jalali A, Ha FJ, Chong G, et al. Hodgkin lymphoma: an Australian experience of ABVD chemotherapy in the modern era. Ann Hematol. 2016; 95: 809-816.
20. Mottok A, Steidl C. Biology of classical Hodgkin lymphoma: implications for prognosis and novel therapies. Blood. 2018; 131: 1654-1665.

21. Eberle FC, Salaverria I, Steidl C, et al. Gray zone lymphoma: chromosomal aberrations with immunophenotypic and clinical correlations. Mod Pathol. 2011; 24: 1586-1597.
22. Eberle FC, Rodriguez-Canales J, Wei L, et al. Methylation profiling of mediastinal gray zone lymphoma reveals a distinctive signature with elements shared by classical Hodgkin's lymphoma and primary mediastinal large B-cell lymphoma. Haematologica. 2011; 96: 558-566.
23. Zhao XF. Pitfalls in diagnostic hematopathology – Part II. Int J Clin Exp Pathol. 2009; 3: 39-46.
24. Iwaki N, Sato Y, Kurokawa T. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma without mediastinal disease: mimicking nodular sclerosis classical Hodgkin lymphoma. Med Mol Morphol. 2013; 46: 172-176.
25. Gualco G, Natkunam Y, Bacchi CE. The spectrum of B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma: a description of 10 cases. Mod Pathol. 2012; 25: 661-674.
26. Sarkozy C, Molina T, Ghesquières H, et al. Mediastinal gray zone lymphoma: clinico-pathological characteristics and outcomes of 99 patients from the Lymphoma Study Association. Haematologica. 2017; 102: 150-159.
27. Wang HW, Balakrishna JP, Pittaluga S, Jaffe ES. Diagnosis of Hodgkin lymphoma in the modern era. Br J Haematol. 2019; 184: 45-59.