

Hodgkin Lymphoma Mimicking a Large Soft Tissue Sarcoma of The Shoulder: The Essential Role of Immunohistochemistry in Histopathological Diagnosis

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Abstract

The shoulder and axillary regions contain various complex anatomical structures in close proximity, many of which can give rise to neoplasms. Determining the origin and hence the exact diagnosis of advanced (diffuse) tumours in this region may become problematic. In view of the tumour morphology and the affected location in this case, we highlighted the importance of Hodgkin lymphoma immunohistochemistry interpretation in a tumour which was initially suspected to be a soft tissue sarcoma.

Keywords: *hodgkin, immunohistochemistry, sarcoma*

Introduction

Immunohistochemistry (IHC) is a collective term used for various methods utilized to identify tissue constituents as antigens by means of corresponding colour-tagged antibodies. The result enables pathologists to recognize the tissue cells origin. In addition, it may specify cells' function in vivo if one poses the right questions by means of selecting the correct antibodies.

The complex anatomy of the shoulder and axillary regions results in the presence of numerous tissue types located in close proximity. When a diffuse neoplasm arises in this area, there may be difficulty in concluding both the clinical and histopathological diagnosis.

Soft tissue sarcomas and lymphomas are among the malignant neoplasms which can be seen in these regions. Differentiation between these tumour types is based on clinical findings, radiological features, and histopathology.

Hodgkin lymphoma (HL) most often occurs at latero-cervical region (75%), followed by mediastinal, axillary, and para aortic region. Peripheral extranodal involvement is very rare (1). While the onset of HL is typically nodal,

it can secondarily affect extranodal tissue and surrounding organs. This presentation may mimic a soft tissue sarcoma (1). It typically displays a bimodal age distribution with the first peak occurring at 10 to 35 years of age (1). The site of involvement and the age at presentation generally pose a suspicion of HL.

The histopathological distinction between lymphoma and soft tissue sarcoma is routinely determined by IHC. Leucocyte common antigen (LCA) (lymphoid marker) and vimentin (mesenchymal marker) are commonly used for this purpose. However, in the case of HL, the malignant cells display a peculiar IHC pattern.

Non-Hodgkin lymphomas (NHL) are classically composed of a clonal monomorphic population of neoplastic lymphoid cells. This appearance is quite different to HL which comprises of a minority of neoplastic cells in a majority background reactive inflammatory cells. The diagnosis of HL is primarily based on the identification of characteristic multinucleated giant neoplastic cells within an inflammatory milieu. These cells are called Reed-Sternberg (RS)

cells or Hodgkin cells in their mononuclear forms. The RS cells and their variants only constitute between 1% to 10% of the entire cell population. The IHC patterns displayed by HL are quite different to that of NHL. Unlike most lymphoid malignancies, RS cells and Hodgkin cells are not commonly reactive towards LCA. However, they are reactive towards vimentin which is a feature commonly seen in neoplasm of mesenchymal origin especially most soft tissue sarcoma.

In this report, we highlighted the important role of IHC in the diagnosis of HL which occurred in the shoulder region, an area predominantly occupied by soft tissue.

Case report

A 35-year-old man presented with a diffuse right shoulder and anterior chest mass. It had been present for the past one year with progressive enlargement over recent months and was associated with occasional mild pain. On physical examination, the mass was poorly defined with a smooth outer surface (Figure 1). The mass was warm with prominent dilated cutaneous veins and was fixed to the underlying structures. He suffered significant limitation of shoulder movement. Clinically, a soft tissue sarcoma infiltration was suspected.

MRI revealed a diffuse infiltrative tumour mass involving right shoulder musculatures (rotator cuff, deltoid, pectoralis, trapezius, and rhomboids muscles) (Figure 2a). The right subclavian vessels were encased by the tumor with extension along the brachial plexus. Other



Figure 1: The arrows pointed to a large and diffuse swelling involving the right shoulder and the anterior chest wall. The swelling displayed smooth outer surface with ill-defined outer margin. Congested cutaneous veins were evident on the outer skin.

findings include erosion to the adjacent scapula, right humerus medullary involvement, and multiple lymphadenopathy (cervical, axillary, and mediastinal). During admission, the patient's condition was complicated by recurrent symptomatic pleural effusions which required several pleural aspirations.

Biopsy of the right shoulder lesion showed scattered atypically large mononuclear and pleomorphic neoplastic cells with an inflammatory background (Figure 2b). Initial IHC showed neoplastic cells reactivity towards vimentin but non-reactive towards LCA (Figure 3). Further IHC markers showed the neoplastic cells were reactive towards CD30 and CD15 (Figure 3). The cells were however, non-reactive towards anaplastic lymphoma kinase (ALK) protein. The final diagnosis of Mixed cellularity Hodgkin lymphoma (MCHL) variant was made. The neoplastic cells were also noted to be non-reactive towards cytokeratin, cytokeratin 7, epithelial membrane antigen (EMA), smooth muscle actin, desmin, HMB45 (melanoma marker), CD31 (vascular marker), CD34 (fibrohistiocytic marker), CD1a (dendritic cell marker), CD₃ (T cell marker), and CD₂₀ (B cell marker).

Discussion

Classical HL composes 95% of all HL cases (1). In general, classical HL may start unifocally by affecting a single lymph node or a single group of lymph nodes. It commonly spreads by contiguity as seen in this case with cervical, axillary, and mediastinal lymphadenopathy. It can also exhibit focal involvement within a lymph node (2).

About 15 to 25% of classical HL is MCHL. This histotype commonly affects the whole or large areas of lymph nodes with disruption of the normal lymph node architecture (2). The invasion process is typically diffuse rather than nodular (2). It is possible that in this case the tumour had totally destroyed the underlying lymphoid tissue and invaded the surrounding soft tissue. This pattern of invasion may closely mimic sarcomatous infiltration. At this region, Meterissian et al. noted various sarcoma subtypes including malignant peripheral nerve sheath tumour, desmoids tumour, malignant fibrous histiocytoma, myxoid liposarcoma, chondrosarcoma, and fibrosarcoma (3).

The patient's age at presentation was a clinical pointer in arriving at the final diagnosis. HL demonstrates bimodal age distribution curve with the first peaks at 15 and 34 years and second

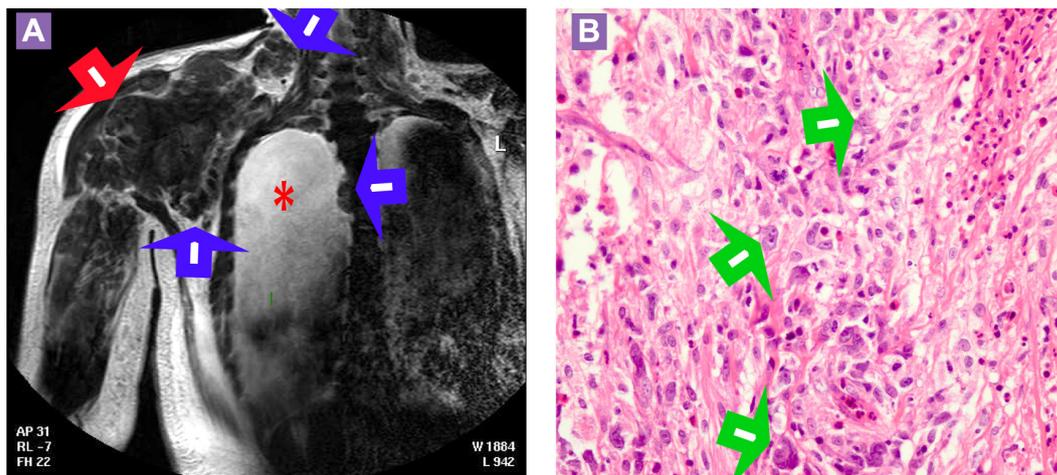


Figure 2: (A) Coronal T2-weighted MR image shows a large diffuse soft tissue mass involving the right shoulder musculatures (red arrow). The mass was associated with marrow involvement of the adjacent right humerus (not shown) and multiple cervical, mediastinal, and axillary lymph nodes (blue arrows). There is also thoracic involvement with presence of pleural effusion (asterisk) and multiple lung nodules on chest radiograph (not shown). (B) Microscopic picture of the tumour mass biopsy. The green arrows point to Hodgkin cells scattered amongst mixed population of inflammatory cells background. The neoplastic cells are mainly mononuclear plump and large with moderate amount of cytoplasm. Nuclear pleomorphism, irregular nuclear membrane, and prominent single large nucleolus are noted. No typical Reed-Sternberg cells noted. The inflammatory cells include lymphocytes, eosinophils, and neutrophils. The pleomorphic nature of the neoplastic cells may mimic pleomorphic sarcoma cells (H & E 40× magnification).

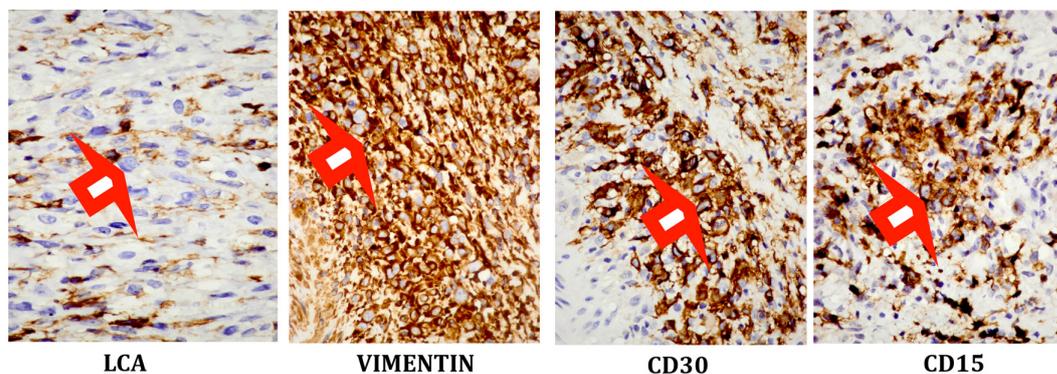


Figure 3: Immunohistochemistry staining on the neoplastic cells. The arrows points to the Hodgkin cells which lacked of LCA staining despite the lymphoid nature of the cells. Strong reactivity of the Hodgkin cells together with the underlying connective tissue for vimentin was observed even though the Hodgkin cells were non-mesenchymal in origin. CD30 and CD15 immunohistochemistry staining on the Hodgkin cells showed typical membraneous and paranuclear globules positivity pattern. CD30 and CD15 reactivity with lack of ALK protein positivity (not shown) pointed to Hodgkin lymphoma diagnosis.

peaks at 54 years (2). In this case the patient's age together with the site of involvement were consistent with the diagnosis of MCHL. Most soft tissue sarcomas occur in patients of older age group.

The MRI findings were consistent with reported features of skeletal muscle lymphoma infiltration. These features include muscle enlargement and mass formation, long segmental involvement along muscle fascicles, intramuscular traversing vessels, intermediate signal intensity on T2-weighted image, and diffuse infiltrative nature involving multiple muscle groups (4). The striking feature of this tumour mass was the hypointensity on T2-weighted images. T2 hypointensity can be seen in fibrosarcoma and lymphoma due to their fibrotic component and hypercellularity. The associated lymphadenopathy which is rarely seen in soft tissue sarcoma favours lymphoma as the diagnosis.

The presence of RS cells and Hodgkin cells is considered a *sine qua non* for the diagnosis of HL (2). These cells however, may show morphological variations and some cells may demonstrate similarity to them in some unrelated conditions. These conditions include infectious mononucleosis, toxoplasmosis, post-vaccinal lymphadenitis, and some neoplasms (2). Thus, the presence of an appropriate cellular inflammatory background and the IHC pattern are the basis for the diagnosis.

The CD45 clusters of antibodies recognized a family of protein expressed on the surface of almost all hematolymphoid cells called LCA (1,5). In classical HL, immunoreactivity towards LCA is rare (5). On the other hand, vimentin expression has been traditionally accepted as specific for cells derived from mesenchymal origin. The Hodgkin cells immunoreactivity towards vimentin may mistakenly lead to the diagnosis of a sarcoma infiltration. In our case, the Hodgkin cells were also noted to be non-reactive towards B and T cell markers.

With respect to the mixed inflammatory cells background, other neoplastic and inflammatory conditions may exhibit features that closely mimic HL. Inflammatory fibrosarcoma, anaplastic large cell lymphoma, T cell/histiocyte rich large B cell lymphoma, primary mediastinal large B cell lymphoma, Lennert's lymphoma (peripheral T cell lymphoma), chronic granulomatous inflammation, and chronic mediastinitis may cause diagnostic problem (1). This problem is further aggravated if the Hodgkin cells are predominantly of mononuclear variant rather

than the classical mirror-image RS cells. Nevertheless, with strict morphological and IHC criteria for recognition of Hodgkin cells, this problem can be avoided (2).

CD30 and CD15 are not entirely specific for RS or Hodgkin cells. Expression of CD30 and CD15 molecules by Hodgkin cells are seen in more than 98% and about 80% of all classical HL (1). CD30 helps to identify Hodgkin cells by its distinctive IHC staining pattern. The typical positive staining pattern is membranous with strong paranuclear globule in the region of Golgi together with weak cytoplasmic staining (5). Cytoplasmic staining alone may be spurious as it can be seen in several non-hematolymphoid neoplasms. This should not be considered as positive staining. One should be aware of other CD30-positive neoplasms such as anaplastic large cell lymphoma, immunoblastic lymphoma, mycosis fungoides, some peripheral T cell lymphoma, plasmacytoma, Langerhans cell histiocytosis, and embryonal carcinoma (5). Anaplastic large cell lymphoma which may resemble HL is conversely reactive towards LCA, EMA, and ALK protein. CD15 staining is commonly non-reactive in this disease.

As in CD30, CD15 staining on Hodgkin cells also displays distinctive membrane and cytoplasmic staining with globular juxtannuclear staining of Golgi. Almost all RS cells and mononuclear Hodgkin cells variants are reactive towards CD15. The characteristic CD15 positivity pattern is crucial in excluding other differential diagnoses. Other CD15 positive neoplasms include myeloid leukaemias, some low-grade B cell lymphoma, granulocytic sarcoma, and some carcinomas (5).

The evaluation of HL may be further aided by other IHC markers. These markers include TNF receptor-associated factor 1 (TRAF1) protein, fascin (a marker for dendritic cells), and EBV infection membrane protein 1 (LMP1). HL is likely to be EBV-positive in very young patients, very old patients, and HIV infected patients (2). These markers were not used in our setting due to practical constraints.

The overlapping immunoreactivity features in IHC necessitate utmost consideration in every histopathological diagnosis. Several neoplasms may show peculiar clinical and histomorphological pattern regardless the cell-lineage origin of the tissue. The definitive diagnosis must take into account the clinical presentation and correlations with the radiological imaging features.

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Authors' Contribution

Conception and design, drafting of the article, and critical revision of the article for important intellectual content: ZAI

Drafting of the article and final approval of the article: MZAN, DNAO

Final approval of the article and provision of study materials or patients: CWH, LHL

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