Case Report

Change in the diagnosis from classical Hodgkin's lymphoma to anaplastic large cell lymphoma by ^{18}F flourodeoxyglucose positron emission tomography/computed tomography: Importance of recognising disease pattern on imaging and immunohistochemistry

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ABSTRACT

Anaplastic large cell lymphoma (ALCL) is a rare type of nonHodgkin's lymphoma (NHL), but one of the most common subtypes of T-cell lymphoma. It is an aggressive T-cell lymphoma, and some ALCL may mimic less aggressive classical HL histopathlogically. It may be misdiagnosed unless careful immunohistochemical examination is performed. As the prognosis and management of these two lymphomas vary significantly, it is important to make a correct diagnosis. We describe a case who was diagnosed as classical HL by histopathological examination of cervical lymph node, in whom ^{18}F-flouro deoxyglucose positron emission tomography/computed tomography appearances were unusual for HL and warranted review of histopathology that revealed anaplastic lymphoma kinase-1 negative anaplastic large T-cell lymphoma, Hodgkin-like variant, thereby changing the management.

Keywords: Anaplastic large cell lymphoma, Hodgkin's lymphoma, ^{18}F-flouro deoxyglucose positron emission tomography/computed tomography

INTRODUCTION

Anaplastic large cell lymphoma (ALCL) is a rare type of T-cell lymphoma. It accounts for about 5% of all cases of nonHodgkin's lymphoma (NHL) and 10–30% of childhood lymphomas.[1] It can involve nodes, and also extranodal sites such as the Waldeyers ring, skin, lung, bone, soft tissue, respiratory and gastrointestinal tract.[2] Depending on the anaplastic lymphoma kinase (ALK-1) expression, it is classified as ALK-1-positive ALCL and ALK-1-negative ALCL.[3] ALK-1-negative ALCL are usually composed of larger pleomorphic cells and because of its anaplastic nature and wide morphological spectrum, it is likely to be misdiagnosed as classical HL, predominantly nodular sclerosis and lymphocyte depletion types. ALCL can also have overlapping cytomorphologic features with T-cell rich B-cell lymphoma. In such cases, the immunohistochemical (IHC) studies would be of great importance in identifying this NHL

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subtype.[1] As the prognosis and management of ALCL and HL differ significantly, it is important to make a correct diagnosis before starting the treatment. We describe a case who was diagnosed as classical HL by histopathological examination of cervical lymph node, in whom the atypical appearances of ^{18}F-flouro deoxyglucose positron emission tomography/computed tomography (FDG PET/CT) for HL lead to the review of histopathology with additional IHC examination which confirmed a rare diagnosis of ALK-1 negative anaplastic large T-cell lymphoma (Hodgkin-like variant).

CASE REPORT

A 37-year-old female presented with fatigue, fever, weight loss and loose stools for 3 months duration. On examination, few enlarged lymph nodes were found in the left lower cervical and left supraclavicular regions. Biopsy of left cervical lymph node was done, and histopathology by haematoxylin and eosin (H and E) staining revealed Reed-Sternberg (RS) cells with CD30 expression on IHC, suggestive of classical HL. Hence, the patient was referred for ^{18}F-FDG PET/CT for initial staging. PET/CT revealed multiple enlarged hypermetabolic lymph nodes on both sides of the diaphragm involving left lower cervical, left supraclavicular, abdomino pelvic nodes including gastrohepatic, perigastric, periportal, portocaval, peripancreatic, bilateral renal hilar, para aortic, aorto caval, mesenteric, bilateral common iliac and bilateral external iliac regions. There were also extranodal hypermetabolic omental thickening and perihepatic peritoneal deposits along segments IVa, IVb, VIII and porta of liver. In addition, metabolically inactive thin-walled cysts were seen in bilateral adnexae with a metabolically active soft tissue density lesion in the right adnexa. There was free fluid in the pouch of Douglas. Images also revealed diffuse bone marrow (BM) hypermetabolism in the axial and appendicular skeleton with few focal areas of relatively increased FDG uptake in the posterior column of left acetabulum, left ischium as well as metadiaphyseal and intramedullary regions of left femur [Figure 1]. The pattern of metabolically active lesion with peritoneal, mesenteric and omental disease were quite unusual for the given diagnosis of HL, and hence based on the imaging appearances, possibility of NHL was considered. However, in view of the metabolically active soft tissue density lesion in the right adnexa with free fluid in the pouch of Douglas, a second possibility of ovarian malignancy was also considered. Histopathology was reviewed with additional IHC markers that showed negativity for PAX-5 and positivity for CD4, confirming the diagnosis as ALK-1 negative anaplastic large T-cell lymphoma [Figure 2a-e]. BM biopsy (by H and E staining) from the left iliac crest did not reveal any evidence of lymphoma infiltration [Figure 2f]. The patient was therefore treated with hyper cyclophosphamide, vincristine, adriamycin and dexamethasone (CVAD) regime. Interim PET/CT after two cycles of chemotherapy showed a very good partial response to therapy [Figure 3].

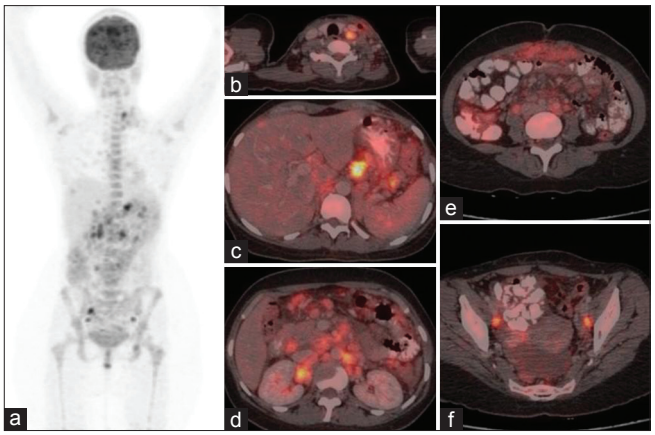

Figure 1: Baseline ^{18}F-flouro deoxyglucose positron emission tomography/computed tomography (a) shows multiple enlarged hypermetabolic lymph nodes on both sides of the diaphragm involving left lower cervical (b), left supraclavicular, abdominal (c and d) and bilateral iliac regions. Diffuse hypermetabolic omental thickening (e) and low grade hypermetabolic perihepatic surface deposits (c) are also seen. In addition, there are metabolically inactive thin walled cysts in bilateral adnexae with a metabolically active soft tissue density lesion in the right adnexa with free fluid in the pouch of Douglas (f)

DISCUSSION

Histologically, ALCL is characterised by sheets of large pleomorphic cells, abundant cytoplasm, horseshoe- or wreath-shaped nuclei and multiple prominent nucleoli. These hallmark tumour cells may be multinucleated and can be similar to RS cells in appearance. Lymphoma cells in ALCL express CD30 antigen (an activation marker for B- or T-cells) on their surface which is also expressed in HL, hence leading to diagnostic dilemma.[4] Therefore, additional IHC markers are needed to differentiate between both the entities.[2] According to the 2008 WHO classification, the most important diagnostic criteria favouring a diagnosis of ALCL are: (i) Nuclear negativity for the PAX-5 transcription factor (usually expressed in classic HL), (ii) negativity for the EBV markers EBER and LMP1 (which may be expressed in classic HL) and (iii) presence of clonal T-cell receptor rearrangements (usually absent in classic HL).[3] Since there is no single marker that is 100% sensitive, it is the best to put the entire set of IHC markers panel to differentiate HL from ALCL, because of the variable T-cell marker expression.

In our patient, the initial diagnosis of classical HL was made with the presence of RS-like cells and strong positivity for CD30 expression. After FDG PET/CT, histopathology was reviewed with additional IHC markers, which revealed negativity for PAX-5 and positivity for CD4, confirming it as ALCL (Hodgkin-like variant). As the ALCL is aggressive form of lymphoma, differentiating it from the HL is important to know the prognosis and aggressively manage with appropriate chemotherapy regime. ALK-1-negative ALCL is a heterogeneous entity which is discrete from ALK-positive ALCL as 75% of former group present as stage IV disease with poor outcome compared to patients with ALK-1-positive disease even though

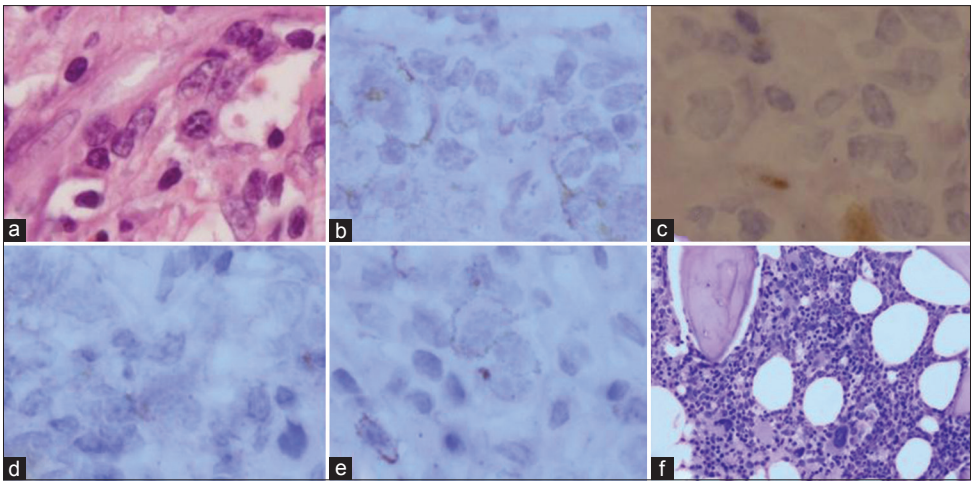

Figure 2: Haematoxylin and eosin staining of cervical lymph node shows Reed-Sternberg-like cells (a). Immunohistochemistry shows CD30 membrane and Golgi positivity (b), PAX-5 negativity (c), focal membranous and cytoplasmic CD4 positivity (d), epithelial membrane antigen membranous positivity (e) in Reed-Sternberg-like cells. Haematoxylin and eosin staining of bone marrow shows normal haematopoietic elements without Reed-Sternberg-like cell infiltration (f)

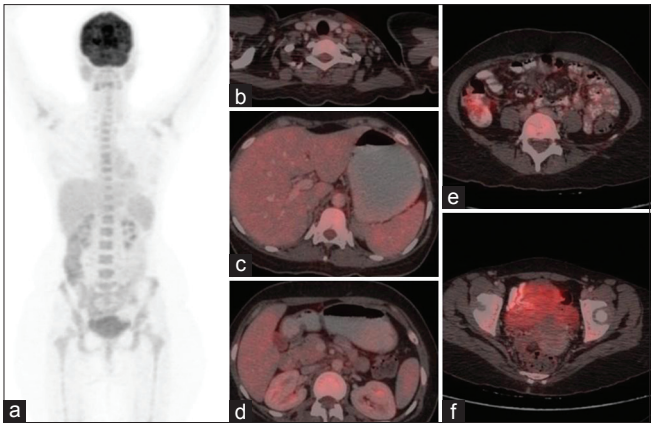

Figure 3: Interim ^{18}F-flouro deoxyglucose positron emission tomography/computed tomography (a) performed after 3 cycles of chemotherapy shows almost complete resolution of multiple enlarged hypermetabolic lymph nodes on both sides of the diaphragm (b-d), diffuse hypermetabolic omental thickening (e) and perihepatic (c) surface deposits and significant reduction in the size of bilateral adnex al cysts with resolution of hypermetabolic soft tissue density lesion in the right adnexa as well as free fl uid in the pouch of Douglas (f)

it has better prognosis than peripheral T-cell lymphoma. Most patients with ALK-1-negative ALCL will relapse and may need more aggressive chemotherapy.[1,3]

Our patient was initially treated with standard ABVD chemotherapy based on the initial diagnosis of HL on histopathology report. However, after careful review of PET-CT findings and clinical presentation, case was re-reviewed for the diagnosis of Hodgkin's lymphoma that was very much unlikely. The extended immunohistochemistry evaluation concluded the diagnosis of ALK-negative ALCL. The management was thereafter changed to hyper CVAD regime. Where in patient received 4 cycles of hyper CVAD regime along with G-CSF support every 3 weeks. Additional intrathecal chemotherapy (methotrexate and cytarabine) was administered for CNS prophylaxis. In view of poor tolerance to chemotherapy, treatment was switched over to CHOP regime, followed by involved field radiation to bulky abdominal residual nodes.

The PET-CT showed diffuse marrow involvement with focal areas of relatively increased FDG uptake in few sites implying focal areas of BM involvement, even though BM biopsy from the iliac crest was negative. Follow-up PET-CT after two cycles of chemotherapy showed resolution of the previously seen irregular foci of marrow uptake. Since BM involvement can be subtle with only scattered malignant cells, it may be easy to miss by routine BM examination.[2] This case therefore also highlights the role of PET in detecting BM involvement in NHL and need for image guided repeat BM biopsy from hypermetabolic marrow sites with negative initial iliac crest BM biopsy.

It is important to consider ALCL in the differential diagnosis of lesions characterised predominantly by discohesive, pleomorphic cells with anaplasia/horseshoe-shaped/wreath-like nuclei because ALCL is a highly treatable form of lymphoma with good 5 years survival rate if it is recognised early and treated appropriately.[5]

CONCLUSION

FDG PET/CT helped in identifying a rare diagnosis of ALK-1 negative anaplastic large T-cell lymphoma, Hodgkin-like variant; and helped in timely change in management who would have been inadvertently treated like classical HL. This case also reaffirms the importance of recognising various patterns of disease involvement during the interpretation of imaging such as PET/CT.

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Conflicts of interest
There are no conflicts of interest.

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