Case Report

Cytokeratin positive anaplastic large cell lymphoma: Difficulty in differentiation from metastatic carcinoma

Nishat Afroz, Divya Rabindranath, Mehar Aziz, Azka Anees Khan

Department of Pathology, J.N. Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India

ABSTRACT

Cytokeratin and epithelial membrane antigen (EMA) are usually included in the first panel of immunomarkers used to differentiate metastatic carcinoma from lymphoma in cases presenting with enlarged lymph nodes. While carcinomas are cytokeratin and EMA positive, most lymphomas are negative for the above. However, recently few cases of cytokeratin positive lymphomas have also been reported. Here, we describe a very rare case of cytokeratin positive anaplastic large cell lymphoma (ALCL) masquerading as a poorly differentiated carcinoma. Simultaneously, we also discuss the differential diagnosis and difficulty in differentiation from metastatic carcinoma in such a scenario. Review of literature shows that this is probably the first case report of anaplastic lymphoma kinase negative-ALCL seen in a young adult.

Key words: Anaplastic, anaplastic lymphoma kinase negative, cytokeratin, lymphoma, metastatic carcinoma

INTRODUCTION

Cytokeratins belong to the intermediate filament family of proteins and form very important tools in diagnostic immunohistochemistry. Upon release from proliferating or apoptotic cells, they form useful markers for epithelial malignancies, distinctly reflecting on going cell activity.[1] Recent reports have reported cytokeratin positivity in few nonepithelial malignancies also. We report a very rare case of anaplastic large cell lymphoma (ALCL) which showed cytokeratin positivity and was initially misdiagnosed as a poorly differentiated carcinoma at a private clinic. To our knowledge, this is the first case report of an anaplastic lymphoma kinase (ALK) negative ALCL seen in a young adult.

Address for correspondence: Dr. Divya Rabindranath, Department of Pathology, J.N. Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India.
E-mail: divy30@hotmail.com

Access this article online

Quick Response Code:

Website: www.ccij-online.org

DOI: 10.4103/2278-0513.168513

CASE REPORT

A 20-year-old Indian female presented with a solitary swelling in neck region for 8 months in the Department of Surgery, Jawaharlal Nehru Medical College Hospital, Aligarh Muslim University. It was nontender and progressively increasing in size. The swelling was associated with fever and lethargy. The patient had undergone a 6-month long anti-tubercular course in the past. On examination, pallor was present, and a single 3 cm × 3 cm level II lymph node was seen enlarged on the right side of the neck. Another 1 cm × 1 cm level V lymph node was also seen to be enlarged. Both swellings were firm, mobile and nontender. No other lymph nodes were seen to be enlarged anywhere else in the body. Subsequently, the patient underwent a fine needle aspiration followed by excisional biopsy of the enlarged cervical node.

Cite this article as: Afroz N, Rabindranath D, Aziz M, Khan AA. Cytokeratin positive anaplastic large cell lymphoma: Difficulty in differentiation from metastatic carcinoma. Clin Cancer Investig J 2015;4:734-6.

Investigations

The patient had already been diagnosed as a case of poorly differentiated carcinoma on histopathological examination of the node done at a private clinic. Cytological examination following fine needle aspiration at our center revealed findings consistent with the diagnosis of poorly differentiated carcinoma. Hematoxylin and eosin sections of the paraffin blocks received showed complete replacement of the normal architecture by diffusely infiltrating large malignant cells. The cells were arranged in a cohesive manner and showed morphology characteristic of "hallmark cells" with vesicular nuclei and prominent nucleoli [Figure 1a and b]. At places, binucleated and multinucleated cells were also seen. The overall morphology was seen to be consistent with a large cell type non-Hodgkin's lymphoma (with a subtype of either diffuse large B-cell/ALCL). The differential diagnosis considered was an undifferentiated carcinoma metastatic to the lymph node.

The patient underwent whole body scan to rule out the possibility of metastatic carcinoma. The scan failed to reveal any masses in the aerodigestive tract, thyroid, and salivary glands or lungs. Serum tumor markers including cancer antigen 19-9 (CA 19-9), carcinoembryonic antigen, and CA-125 were also found to be negative.

We employed the following lymphoid markers on the tissue: CD45, CD10, CD3, CD5, CD15, CD20, ALK, and CD30. Besides these, epithelial markers such as pan-cytokeratin and epithelial membrane antigen (EMA) were also used along with S100, HMB 45, CD34, CD99, and synaptophysin. On immunohistochemistry, the tumor cells showed diffuse, moderate to strong reactivity to pancytokeratin [Figure 1c]. They showed equivocal to negative reactivity to CD45 antigen, in comparison to surrounding lymphoid tissue [Figure 1d]. CD30 (Ki-1) was mostly positive in the tumor cells [Figure 1e]. The rest of the markers were negative including ALK [Figure 1f].

Based on the histopathology and immunohistochemistry findings, a putative diagnosis of low-grade ALCL (Stage 1A) was made.

Differential diagnosis

The most important differential diagnosis in our case was metastatic carcinoma. Other lesions which should be differentiated from ALCL include classical Hodgkin's lymphoma, melanoma, peripheral T-cell lymphoma not otherwise specified, other malignant lymphomas, histiocytic sarcoma, and embryonal carcinoma

Treatment

The patient underwent chemotherapy in the form of CHOP regime and was discharged in a satisfactory condition. She has completed two cycles of the regime, each cycle of 21 days with an intravenous dose of cyclophosphamide, doxorubicin, and vincristine on day 1 and an oral dose of prednisone on days 1–5. She is progressing well and did not reveal any fresh complaints on follow-up.

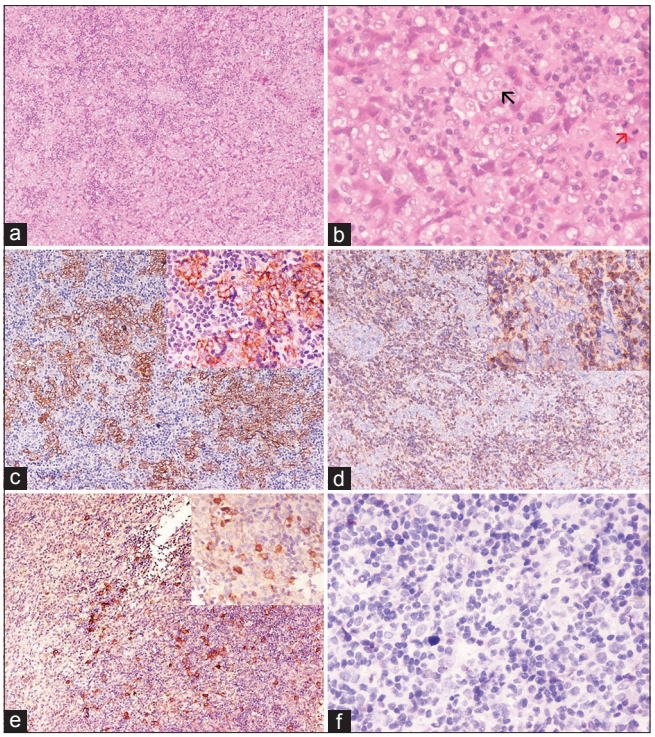

Figure 1: (a) Photomicrograph is showing diffusely infiltrating large malignant cells arranged in a cohesive manner, completely effacing the normal architecture (H and E, ×10). (b) Characteristic "hallmark" cells-large with an eccentrically placed embryo-like or reniform nucleus, multiple prominent eosinophilic nucleoli (black arrow) and abnormal mitotic figure (red arrow) (H and E, ×40). (c) Tumor cells show diffuse, moderate to strong reactivity to pancytokeratin (IHC CK, ×10) inset - IHC CK, ×40. (d) Tumor cells show negative reactivity to CD45 antigen, in comparison to surrounding lymphoid tissue (IHC CD45, ×10, inset - IHC CD45, ×40). (e) CD30 (Ki-1) seen mostly positive in the tumor cells (IHC CD30, ×10, inset - IHC CD30, ×40). (f) ALK/P80 immunohistochemistry shows negative staining in the neoplastic cells (IHC ALK, ×40)

DISCUSSION

ALCL is a CD30 + lymphoma of T- or null-cell lineage, characterized by large cells with voluminous cytoplasm, although variants composed of smaller cells are also recognized.[2] It was first recognized by Stein *et al*. in 1985,[3] who described 45 cases with CD30 (Ki-1 antigen) expression and prominent sinusoidal invasion that had been previously diagnosed as malignant histiocytosis or anaplastic carcinoma. The histopathological picture is defined by the presence of characteristic, but not pathognomonic cells called hallmark cells.[4] These are large cells with an eccentrically placed embryo-like or reniform nucleus, a distinct eosinophilic Golgi zone in the ample cytoplasm, and multiple small nucleoli.

On immunocytochemistry, T-lineage markers are positive in the T-cell type ALCL, while both T- and B-cell markers are negative in the null cell type. CD30 and EMA are commonly positive,[5] while 50–80% cases of ALCL are ALK positive. HLA-DR and CD25 are also commonly positive.[5] A proportion of cases show CD15 positivity.[5] Up to 38% cases of ALCL can show negativity for CD45,[5] and rare cases show cytokeratin positivity.[6] EMA is usually positive in most cases of ALCL and hence, cannot be used to differentiate it from metastatic carcinoma.

The discovery of t (2; 5) as a cytogenetic marker of ALCL and characterization of the implicated genes (NPM and ALK) have led to the conclusion that ALK-positive ALCL forms a distinct entity.[4] This group is called as "ALCL, T- or null-cell, primary systemic form, ALK+" or "ALKoma" in short.[7] This homogenous entity has certain characteristic features including younger age of presentation with single age peak in the third decade, presentation with primary systemic disease, frequent EMA expression and highly favorable prognosis,[8] while ALK negative ALCL are usually elderly adults beyond fifth decade, frequent relapses within 5 years and poor prognosis with 5-year survival rate of 30–46%, thereby warranting a stem cell transplant after remission.[8]

While cytokeratin is traditionally used to delineate epithelial malignancies, previous studies have shown that cytokeratin can also be expressed in nonepithelial malignancies such as epithelioid sarcoma, epithelioid angiosarcoma,[9] synovial sarcoma, mesothelioma, chordoma, and some lymphomas.[10] Gustmann *et al.*,[6] demonstrated that about 27% (5/18) ALCL showed positivity for cytokeratin.

Another morphological feature of ALCL that leads to confusion with metastatic carcinoma is its tendency for sinusoidal involvement, which is normally also seen in metastatic carcinoma or melanoma. It has been proposed that electron microscopic examination can be helpful to differentiate between ALCL and metastatic carcinoma in such cases by showing the characteristic electron microscopy features of epithelial differentiation, such as tonofibrils and desmosomes in cases of metastatic carcinoma.[11]

Hence, such a case with confusing morphological features, and unconventional immunoprofile with cytokeratin positivity and negativity for CD45 can easily be misdiagnosed as a case of metastatic carcinoma. However, close attention to the histopathological features including the presence of characteristic hallmark cells, along with CD30 positivity on immunostaining should alert the pathologist to a diagnosis of ALCL.

Take home messages

Metastatic carcinoma forms the usual differential diagnosis in cases of ALCL, because of their similar histological appearance, and the presence of a sinusoidal pattern of involvement which is common to both.

While cytokeratin is usually expressed in epithelial malignancies, it can also be rarely expressed in few cases of ALCL. This leads to further confusion in the diagnosis of such cases.

CD30 positivity along with close attention to morphological features can help in reaching the correct diagnosis in such a scenario.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Barak V, Goike H, Panaretakis KW, Einarsson R. Clinical utility of cytokeratins as tumor markers. Clin Biochem 2004;37:529-40.
2. Chott A, Kaserer K, Augustin I, Vesely M, Heinz R, Oehlinger W, *et al.* Ki-1-positive large cell lymphoma. A clinicopathologic study of 41 cases. Am J Surg Pathol 1990;14:439-48.
3. Stein H, Mason DY, Gerdes J, O'Connor N, Wainscoat J, Pallesen G, *et al.* The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: Evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. Blood 1985;66:848-58.
4. Benharroch D, Meguerian-Bedoyan Z, Lamant L, Amin C, Brugières L, Terrier-Lacombe MJ, *et al.* ALK-positive lymphoma: A single disease with a broad spectrum of morphology. Blood 1998;91:2076-84.
5. Delsol G, Al Saati T, Gatter KC, Gerdes J, Schwarting R, Caveriviere P, *et al.* Coexpression of epithelial membrane antigen (EMA), Ki-1, and interleukin-2 receptor by anaplastic large cell lymphomas. Diagnostic value in so-called malignant histiocytosis. Am J Pathol 1988;130:59-70.
6. Gustmann C, Altmannsberger M, Osborn M, Griesser H, Feller AC. Cytokeratin expression and vimentin content in large cell anaplastic lymphomas and other non-Hodgkin's lymphomas. Am J Pathol 1991;138:1413-22.
7. Falini B, Pileri S, Zinzani PL, Carbone A, Zagonel V, Wolf-Peeters C, *et al.* ALK lymphoma: Clinico-pathological findings and outcome. Blood 1999;93:2697-706.
8. Ferreri AJ, Govi S, Pileri SA, Savage KJ. Anaplastic large cell lymphoma, ALK-negative. Crit Rev Oncol Hematol 2013;85:206-15.
9. Agaimy A, Kirsche H, Semrau S, Iro H, Hartmann A. Cytokeratin-positive epithelioid angiosarcoma presenting in the tonsil: A diagnostic challenge. Hum Pathol 2012;43:1142-7.
10. McCluggage WG, el-Agnaff M, O'Hara MD. Cytokeratin positive T cell malignant lymphoma. J Clin Pathol 1998;51:404-6.
11. Eyden B, Chakrabarty B, Hatimy U. Carcinoma versus cytokeratin-positive lymphoma: A case report emphasizing the diagnostic role of electron microscopy. Ultrastruct Pathol 2009;33:33-8.