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Case Report

Pathology Section

Diffuse Strong Membrane Expression of MIC2 (CD99) in Anaplastic Large Cell Lymphoma: A Diagnostic Challenge

RENU SUKUMARAN[1], JAYASUDHA A VASUDEVAN[2], JAYASREE KATTOOR[3], SUGEETH M THAMBI[4], JIJU GEORGE ZACHARIAH[5]

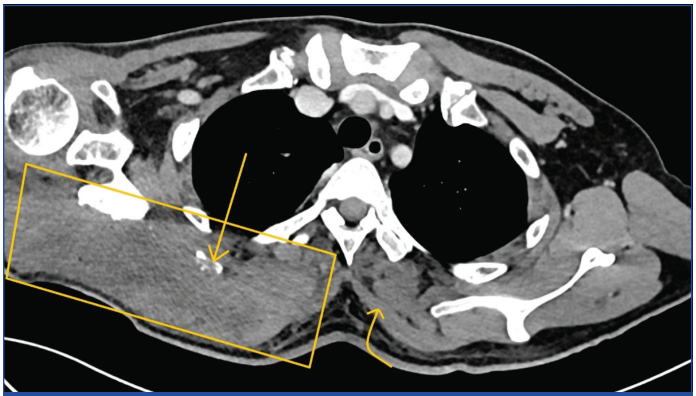
ABSTRACT

The MIC2 [Cluster of Differentiation 99 (CD99)] has been widely used in making the diagnosis of Ewing's sarcoma and diffuse strong membrane expression is the characteristic finding. The CD99 is a sensitive marker of Ewing's sarcoma, but not specific. Studies have shown expression of CD99 in a wide variety of neoplasms which include epithelial, mesenchymal and haematopoietic neoplasms. In these tumours, the positivity of CD99 is described as variable with focal/patchy, irregular, membrane/cytoplasmic staining. Among the haematopoetic neoplasms, diffuse strong positivity of CD99 is seen in blasts which include T-lymphoblasts, B-lymphoblasts and myeloblasts. Recent studies have demonstrated positive staining of CD99 in mature lymphomas where the pattern of expression is heterogenous and highly variable. Herein, authors report the case of a 42-year-old male patient with expansile destructive lesion in right scapula with large soft tissue component. With clinical diagnosis of sarcoma, biopsy was taken which showed large atypical cells arranged diffusely, focally around vessels and in vague rosettoid pattern. In the initial immunopanel, neoplastic cells showed diffuse strong membrane expression of CD99 and were negative for cytokeratin, synaptophysin, chromogranin, desmin and S100. On further examination, the neoplastic cells showed focal weak to moderate positivity for CD45, diffuse strong positivity for CD30 and strong positivity for Anaplastic Lymphoma Kinase (ALK). Diagnosis of ALK positive Anaplastic Large Cell Lymphoma (ALCL) was given. The awareness of diffuse strong membrane pattern of staining of CD99 in ALCL will help to avoid misdiagnosis especially in cases with atypical clinical presentations.

Keywords: Expansile, Haematopoietic, Neoplasms, T-lymphoblasts

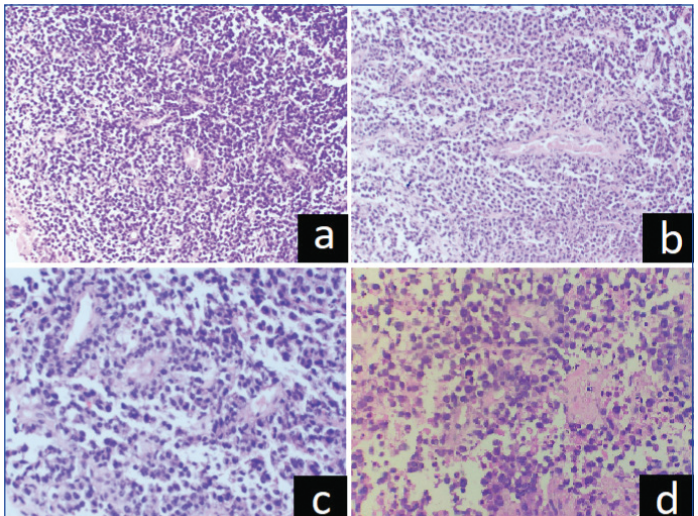
CASE REPORT

A 42-year-old male patient presented with swelling in right scapular region of three month duration. On examination, he had a 14x12 cm swelling in the right scapular region with redness over the shoulder and impaired limb abduction. There was no significant past history. Computerised Tomography (CT) scan showed heterogenous soft tissue mass 12×8×7.5 cm along intramuscular plane involving supraspinatus, infraspinatus and rhomboids causing erosion of spine and body of scapula [Table/Fig-1].



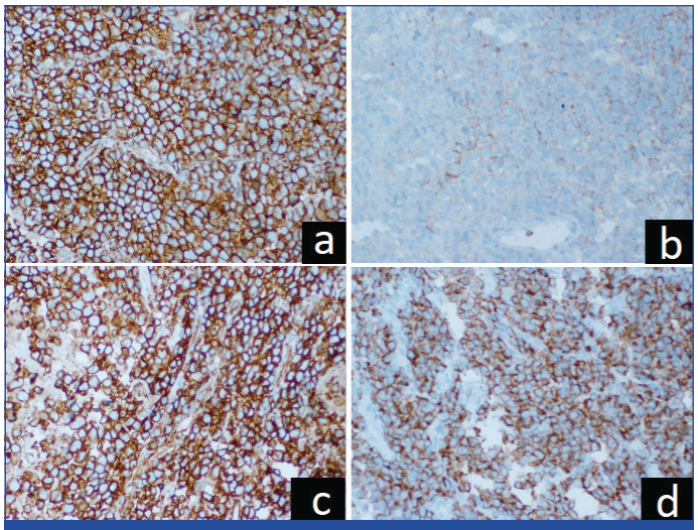
[Table/Fig-1]: Computerised Tomography (CT) scan showing heterogeneous minimally enhancing mass along intramuscular plane involving supraspinatus, infraspinatus and rhomboids causing erosion of spine and body of scapula. (Box-soft tissue mass infiltrating muscle, straight arrow-scapular spine erosion, curved arrow-normal trapezius muscle)

Patient's complete haemogram, renal and liver function tests were within normal limits. Lactate Dehydrogenase (LDH) test was 170 IU/L. Biopsy of the shoulder lesion was done with clinical impression of sarcoma. Microscopy showed neoplasm showing sheets of large atypical cells with moderate amount of pale/vacuolated cytoplasm, enlarged irregular vesicular nuclei, some showing prominent nucleoli. Cells were focally arranged around vessels. Vague rosettoid formations were also noted [Table/Fig-2]. Differential diagnosis included Ewing's sarcoma, rhabdomyosarcoma and clear cell sarcoma. On immunohistochemical examination, the cells showed diffuse strong membranous positivity for CD99 [Table/Fig-3a] and were negative for cytokeratin, synaptophysin, chromogranin, desmin and S100.



[Table/Fig-2]: a,b) Sheets of large atypical cells (H&E, X40 and X100); c) Cells focally arranged around vessels and vague rosettoid formations (H&E, X 200); d) Cells with moderate amount of pale/vacuolated cytoplasm, enlarged irregular vesicular nuclei, some showing prominent nucleoli (H&E, X 400).

In subsequent immunohistochemical study, the neoplastic cells showed focal weak to moderate positivity for CD45 and diffuse strong positivity for CD30 and ALK [Table/Fig-3b-d]. The neoplastic cells were CD20 negative, CD4 positive and showed down regulation of CD5. Diagnosis of ALK positive Anaplastic Large Cell Lymphoma(ALCL) was given.



[Table/Fig-3]: a,b) Neoplastic cells showing diffuse strong membrane expression of CD99 (IHC, 200X); b) Patchy weak positivity for LCA (IHC, 200X); c) Diffuse strong positivity for CD30 (IHC, 200X); d); diffuse positivity for ALK (IHC, 200X).

Bone marrow studies were within normal limits. The patient was planned for chemotherapy-cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate and prednisone (CHOP) for six cycles and radiation to the bulky scapular lesion.

DISCUSSION

The CD99 is a 32-kDa cell surface sialoglycoprotein, encoded by MIC2 gene, a pseudoautosomal gene located in the short arm of the X and Y chromosomes. Functionally, CD99 is involved in differentiation of primitive neuroectodermal cells [1-3]. It has role in mediating T-cell interactions, T cell adhesion, apoptosis of T cells and migration of leukocytes. CD34 positive progenitor cells show CD99 expression. In lymph nodes, activated T-cells cells and memory B-cells may show CD99 up-regulation [2-5].

The CD99 was originally described as a diagnostically useful marker for Ewing's sarcoma/primitive neuroectodermal tumour and diffuse strong membranous expression is the typical finding. Expression of CD99 has been demonstrated in a variety of tumours including epithelial, mesenchymal and haematopoetic tumours. The reported staining patterns in these neoplasms includes membranous and cytoplasmic staining and can be focal or diffuse [2].

The CD99 positivity has been demonstrated in metaplastic breast carcinoma, pleomorphic lung and stomach carcinomas, neuroendocrine tumours, testicular and ovarian sex cord stromal tumours, rhabdomyosarcoma, synovial sarcoma, mesenchymal chondrosarcoma, ependymoma and solitary fibrous tumour [2,6,7].

In haematopoietic system, CD99 is highly expressed in early CD34+ precursors and the expression of CD99 is strongly correlated with TdT expression. CD99 positivity has been observed in T and B-lymphoblastic lymphomas/leukemias, acute myeloid leukemia and in blast crisis of chronic myeloid leukemia. Recent studies have demonstrated heterogenous expression of CD99 in mature lymphomas including ALCL, Diffuse Large B-Cell Lymphoma (DLBCL), Burkitt lymphoma, and CD30 negative peripheral T-cell lymphoma [2,8-11].

ALCL is a T-cell lymphoma characterised by large cells with abundant cytoplasm, and pleomorphic often horse-shoe shaped nuclei. There are two clinical forms of ALCL-primary systemic ALCL and primary cutaneous ALCL. Primary systemic ALCL accounts for 10% to 20% of childhood Non-Hodgkin's Lymphoma (NHL) and approximately 3% of adult NHL [2,12]. Depending on the expression of ALK, systemic ALCL is subcatergorised into ALK-positive and ALK-negative ALCL. The ALK-positive primary systemic ALCL involves lymph nodes and extranodal sites such as skin, soft tissues, lungs, bone and liver. Extranodal involvement is less frequent in ALK negative primary systemic ALCL. Primary cutaneous ALCL is more common in older people and are usually ALK negative [2,12].

Sung CO et al., studied immunoreactivity of CD99 in 182 cases of non-Hodgkin's lymphoma [10]. They observed that all the cases of T-lymphoblastic lymphomas and 60% of B-lymphoblastic lymphomas showed CD99 positivity. The study demonstrated CD99 expression in 54% of ALCLs, 5.4% of DLBCL and 11.1% of Burkitt's lymphomas.

Study by Buxton D et al., observed expression of CD99 in 64.4% cases of ALCL. In their study, immunoreactivity for CD99 was considered positive, if at least 25% of the neoplastic cells demonstrated a membranous pattern of staining [2]. They noted that the CD99 expression was slightly more frequent in ALK positive cases compared with ALK negative cases (80% vs 54%). The staining pattern of CD99 was predominantly membranous with variable intensity.

The awareness of the occurrence of CD99 positivity in tumours other than Ewing's sarcoma is important in rendering accurate diagnosis. Among haematopoetic neoplasms, mature lymphomas can also show significant expression of CD99.

CONCLUSION(S)

While using antibodies such as CD99 for diagnostic purpose, the awareness of expression of this marker in a wide range of neoplasms as well as the significance of staining patterns will help to avoid misdiagnosis. Nodal and extranodal ALCL should also be considered in the differential diagnosis when a CD99 positive neoplasm is encountered.

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PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Pathology, Regional Cancer Centre, Thiruvananthapuram, Kerala, India.
2. Assistant Professor, Department of Pathology, Regional Cancer Centre, Thiruvananthapuram, Kerala, India.
3. Professor, Department of Pathology, Regional Cancer Centre, Thiruvananthapuram, Kerala, India.
4. Assistant Professor, Department of Medical Oncology, Regional Cancer Centre, Thiruvananthapuram, Kerala, India.
5. Senior Resident, Department of Imageology, Regional Cancer Centre, Thiruvananthapuram, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Renu Sukumaran,
Associate Professor, Department of Pathology, Regional Cancer Centre,
Thiruvananthapuram, Kerala, India.
E-mail: renu.sukumaran@gmail.com

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