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CYTOKERATIN POSITIVE FIBROBLASTIC RETICULUM CELL SARCOMA IN A PATIENT WITH GLOMERULONEPHRITIS: ACCIDENTAL OR TRUE ASSOCIATION

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ABSTRACT
Tumours of accessory reticulum cells are rare neoplasms arising mostly in lymph nodal areas. Cytokeratin positive Fibroblastic Reticulum Cell tumour is one such variety which has been reported very rarely in literature. Fibroblastic Reticular Cells (FRC's) are cytokeratin positive Interstitial Reticulum Cells (CIRC's) and a tumour derived from these cells expresses cytokeratin strongly mimicking metastases from a carcinoma. We report a 30 year old woman who presented with chronic glomerulonephritis and worsening of symptoms since a year with the appearance of an inguinal nodal mass. The node showed a spindle cell tumour with expression of cytokeratin that initially gave rise to suspicion of metastases, but as there was no primary detected, the tumour was excised. The lesion was subsequently recognized as a cytokeratin expressing fibroblastic reticulum cell sarcoma. The excision of the tumour resulted in improvement of renal function tests but the patient refused local radiotherapy and since last 9 months she is alive with no disease. Thus we speculate possible causes for the improved condition of patient and the pointers to the accurate histologic diagnosis of this rare entity.

INTRODUCTION

Lymph nodes contain many accessory cells which help in antigen presentation like Follicular Dendritic Cells (FDC's), Interdigitating Dendritic Cells (IDC's), Langerhans cells and Fibroblastic Reticular Cells (FRC's). Cytokeratin positive Interstitial Reticulum Cells (CIRC's) are a type of FRC's. Tumours arising from CIRC's are rare, presenting diagnostic challenges for pathologists and clinicians. While specific markers exist for FDC and IDC, markers for FRC show overlap especially the cytokeratin expression which mimics metastatic carcinoma in nodes. Only around eighteen cases of FRC tumours have been reported in literature till date [1-4]. We report a Cytokeratin Positive FRC sarcoma in a patient with chronic glomerulonephritis where after excision of tumour, renal function tests improved.

Case Report

A 33 year old female patient was under therapy for renal failure due to glomerulonephritis for two years. In the past year, she presented with progressive worsening of clinical symptoms, serous effusions, anasarca and a gradually increasing inguinal swelling. Her serum protein electrophoresis revealed an abnormal M band with beta 2 microglobulin level of 3918 ng/ml. She had BUN of 121mg/dL and severe proteinuria on admission. In spite of being on steroids, her renal condition worsened. After dialysis, biopsy of inguinal nodal mass was done. This biopsy was preliminarily diagnosed as sarcomatoid carcinoma versus dendritic cell sarcoma.

FDG PET Scan revealed FDG avid nodal lesions (max.SUV of 7.93)in right inguinal and obturator regions,

the largest node measuring 4.6x 3.7cm. No other focus of abnormal FDG uptake was seen and there was no other lymphadenopathy or obvious primary tumour. Subsequent to this, excision of mass was done and sent for histopathological examination. Post-surgery there was dramatic improvement in patient's symptoms. Patient refused local radiotherapy for tumour and is fine with improved kidney function since last 9 months.

Pathological Findings

The excised mass was multinodular with grey white cut surface. Histological examination revealed partial effacement of nodal architecture with a distinct focus of spindle cell proliferation composed of bland-looking cells arranged in sheets and fascicles (Figure 1 A & 1B). Individual cells were oval to elongated, with moderate amount of eosinophilic cytoplasm and vesicular nuclei with few inconspicuous nucleoli (Figure 2). Tumour cells showed little or no mitosis. Normal reactive lymphoid tissue was identified in peripheral subcapsular region. The admixed reactive inflammatory cells included plasma cells and eosinophils. No giant cells or necrosis was seen.

On immune histochemistry, the tumour expressed Cytokeratin (CK, MNF 1) in 50 % of cells in tapering, slender pattern, reminiscent of dendritic cell outline (Figure 3). Also, tumour was focally positive for LCA and S-100 Protein. The tumour was negative for dendritic cell markers CD 21 and CD 23. Tumour was negative for Alk1 and CD 30, thus excluding sarcomatoid variant of Anaplastic Large Cell Lymphoma and Inflammatory MyoFibroblastic Tumour.

Additionally, CD 1a (for Langerhans Cell Histiocytosis) and CD 138 (for plasma cells) were negative. A differential diagnosis of dendritic tumour versus metastatic poorly differentiated carcinoma was initially considered based on these findings. Subsequently after PET scan findings, final diagnosis of cytokeratin expressing FRC sarcoma was made.

Fig 1. A) H&E section from nodal mass shows preserved lymph node structure at periphery and a spindle cell proliferation on the right side (H&E : 10).
B) Higher magnification of the spindle cell area with admixed plasma cell and eosinophils(H&E: 100)

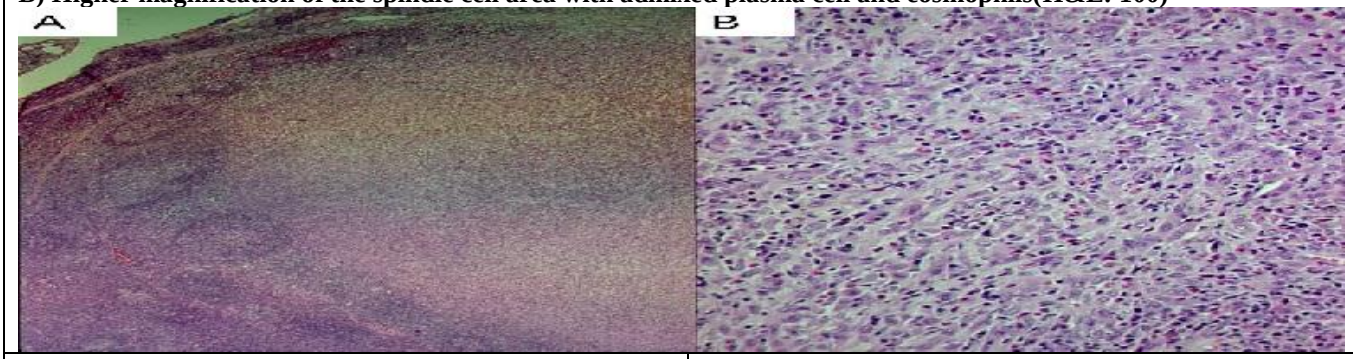


Fig 2. Individual spindle cells have pale chromatin with irregular outline and inconspicuous nuclei or mitosis. (H&E: 400)

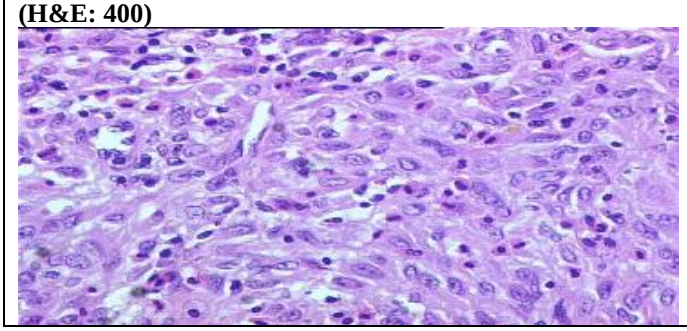
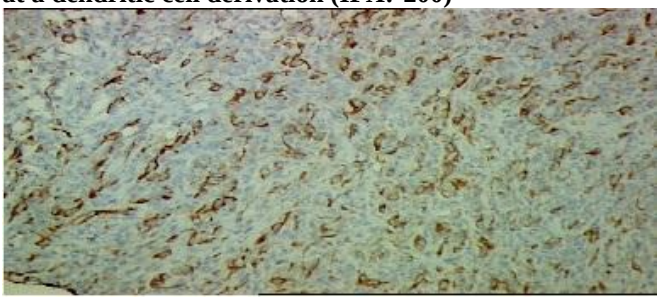


Fig 3. Cytokeratin immunohistochemistry demonstrates the slender tapering processes in the spindle cells hinting at a dendritic cell derivation (IPX:-200)



DISCUSSION

Dendritic cells are antigen-presenting cells that play broad roles in innate and adaptive immunity. Cytokeratin positive Interstitial Reticulum cells (CIRC's) were originally described by Frank and Moll in 1987 [5]. FRC's help in maintaining integrity of lymph nodes and generation of mediators like cytokines for immune responses. CIRC's have slender, long cytoplasmic processes extending between lymphocytes and are present mainly in extrafollicular areas of nodes. They express Cytokeratin 8, 18 and some of them co-express Smooth Muscle Actin, Desmin and S100 protein. Tumours arising from these cells usually occur in nodes, spleen or soft tissues.

The pathogenesis of tumours arising from CIRC's remains largely unknown. Although originally considered as supporting cells in nodes, in recent decades it has been suggested that FRC's may have additional functions, such

as support for lymphocyte migration and survival, activation and control of immune responses and a role in peripheral tolerance [6].

The FRC's can not only induce tolerance in T cells by expression of self-antigens but can also limit T cell response to foreign antigens by expression of suppressive factors leading to direct inhibition of T cells or indirect inhibition by reducing dendritic cells' immunogenicity. FRC's thus are both positive and negative regulators of adaptive immunity and can act as inducers or suppressors in autoimmune diseases [7].

It has been observed that FRC's are derived from mesenchymal stem cells and undergo hyperplasia in response to injury thus forming the background for development of a neoplastic process [8]. Thus hyperplasia of FRC's within nodes occurs in patients with HIV, post infections like toxoplasmosis and in nodes draining cancers. It may also occur in patients with auto immune diseases. These tumours have been found to over express p53 protein [9]. Though Epstein Barr Virus has been suggested to play an aetiological role in these tumours, it has not been proven still. Thus we speculate that chronic antigenic stimulation could have led to expansion of CIRCs in our case and these hyperplastic CIRC's also played some additive functional role in disease development.

Of the 18 odd cases of FRC tumours reported in English literature, four were CK negative and 11 were CK positive (including present case) [4, 9, 10]. Most of the previously reported cases of tumours arising from FRC's have occurred at nodal locations, like our case [4]. Systemic symptoms were uncommon. In lesions arising from nodal areas, presence of large number of spindle cells arranged in storiform pattern should arouse suspicion of tumour arising from FRC's. The ultimate pathological diagnosis depends on histomorphological features, immunostaining pattern and ultrastructural findings. It is necessary to differentiate these tumors from those arising from other accessory dendritic cells, myofibroblasts and metastatic poorly differentiated carcinomas due to marked differences in treatment and prognosis.

Cytokeratin positivity can easily lead to misdiagnosis of carcinoma. However, absence of obvious atypia and mitosis in these cells coupled with characteristic tapering shape of dendritic processes is a clue to accurate diagnosis. Moreover, absence of primary tumour rules out metastatic carcinoma as was seen in our case. Other differentials need to be excluded by appropriate markers.

Surgical excision is the treatment of choice. The role of adjuvant chemotherapy and radiotherapy is not clearly defined as they are best regarded as sarcomas [4]. These tumours have better prognosis as compared to their counterparts like dendritic and histiocytic sarcomas. It is therefore essential that pathologists and clinicians be aware of this rare tumour and make a correct useful diagnosis.

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