A Rare Case of Cytokeratin-Positive Interstitial Reticulum Cell Sarcoma and Review of the Entity

Shravasti Roy · Indranil Das · Kaushik Saha ·
Rakesh Roy · Sumanta Bhattacharya

Received: 9 August 2014 / Accepted: 27 February 2015 / Published online: 11 March 2015
© Indian Association of Surgical Oncology 2015

Abstract The tumors of dendritic/reticulum cells constitutes the rarest tumors affecting the lymphoid tissues. Among them tumors derived from fibroblastic reticular cells (FBRCs) are very rare, and those of cytokeratin (CK)-positive interstitial reticulum cells (CIRC)s origin are even more rare. These tumors can be easily misdiagnosed as tumors of other dendritic cells, myofibroblastic tumors or even metastatic poorly differentiated carcinomas. Less than twenty such cases have been reported in the literature till date. We present such a rare case of CIRC sarcoma in cervical lymph node of a 64-year-old man.

Keywords Reticulum cell · Cytokeratin · Sarcoma · Lymph node · Immunohistochemistry

Introduction

Lymph nodes contain nonlymphoid accessory dendritic/reticulum cells including follicular dendritic cells (FDCs), interdigitating dendritic cells (IDCs), Langerhans cells (LCs)

S. Roy · I. Das · S. Bhattacharya
Department of Pathology, Saroj Gupta Cancer Centre and Research Institute, Thakurpukur, Kolkata, India

K. Saha (✉)
Department of Pathology, Murshidabad Medical College and Hospital, Berhampore, Murshidabad, India
e-mail: drkaushik.saha@yahoo.com

K. Saha
42/9/2, Sashi Bhusan Neogi Garden Lane, Baranagar, Kolkata, India
700 036

R. Roy
Department of Medical Oncology, Saroj Gupta Cancer Centre and Research Institute, Thakurpukur, Kolkata, India

and fibroblastic reticular cells (FBRCs). Cytokeratin (CK)-positive interstitial reticulum cells (CIRC)s are considered to represent a subset of FBRCs. Although the tumors of dendritic/reticulum cells constitutes the rarest tumors affecting the lymphoid tissues, the neoplasms derived from the first three cell types are well documented and relatively known entities. Tumors derived from FBRCs are very rare, and those of CIRC origin are even more rare [1, 2]. They are easily misdiagnosed as tumors originating from other accessory dendritic cells, myofibroblasts or even metastatic poorly differentiated carcinomas due to their similar histomorphologic features [3]. Extensive review of the literature reveals only nineteen cases of FBRC tumors (FBRCTs) including 4 cases of CK-negative FBRCTs, 14 cases of CIRC tumors (CIRCTs) and one case of mixed tumor with dendritic and fibroblastic features, reported till date (Table 1). We report an additional case of CIRCT in cervical lymph node of a 64-year-old man.

Case Report

A 64-year-old male presented with gradually increasing painless swelling in the right submandibular region for last three months without any history of associated rise of temperature. There was no improvement with three courses oral antibiotics which was prescribed by his family physician. On clinical examination, three enlarged painless firm mobile lymph nodes were observed in right submandibular, mid cervical and supraclavicular regions. Out of these three lymph nodes mid cervical lymph node was the largest one. No other relevant abnormality was detected on clinical examination. On routine hematological investigation, his hemoglobin level was 13.2 g/dL, total white blood cell count was 6,700/mm³ and RBCs displayed normocytic normochromic features on peripheral blood film examination. The erythrocyte sedimentation rate (ESR) was 40 mm after the 1st hour and platelet count was

Table 1 Summary of clinicopathological features of the patients with FBRCTs/CIRCTs reported in the literature

Cases	Age/Sex	Location	Positive immunostaining	Cytokeratin expression	Negative immunostaining	Treatment	Follow up	Diagnosis
Case 1 (1990; Gould et al.)	57 year/Male	Mediastinal lymph node	Vimentin, SMA	CK 8, CK 18, CK AE 1/AE 3	S-100, CD45, Desmin	Surgery and radiotherapy	NED, 9 years	CIRCT
Case 2 (1990; Gould et al.)	44 year/Male	Mediastinal lymph node	Vimentin, SMA, Desmin	CK 8, CK 18, CK AE 1/AE 3	S-100, CD45	Surgery	NED, 3 years	CIRCT
Case 3 (1990; Gould et al.)	61 year/Male	Mediastinal lymph node	Vimentin, SMA, Desmin	CK 8, CK 18, CK AE 1/AE 3	S-100, CD45	Surgery and radiotherapy	NED, 13 months	CIRCT
Case 4 (1998; Andriko et al.)	13 year/Male	Supraclavicular lymph node	Vimentin, Desmin, CD68, factor XIII	Negative	S-100, CD1a, CD45, CD20, CD3, CD21, CD35, SMA	Surgery	NED, 8 years	FBRCT
Case 5 (1998; Andriko et al.)	23 year/ Male	Cervical lymph node	Vimentin, SMA, Desmin, CD68, Factor XIII	Negative	S-100, CD1a, CD45, CD20, CD3, CD21, CD35	Surgery and radiotherapy	NED, 2 years	FBRCT
Case 6 (1998; Andriko et al.)	14 year/Female	Epitrochlear lymph node	Vimentin, SMA, Desmin, CD68, Factor XIII	Negative	S-100, CD1a, CD45, CD20, CD3, CD21, CD35	Surgery	N/A	FBRCT
Case 7 (2000; Chan et al.)	21 year/Female	Mediastinal lymph node	Vimentin	CK 8, CK 18, CK AE 1/AE 3	S-100, CD21, CD35, CD68 SMA, Desmin	Chemotherapy and radiotherapy	Died after 9 months	CIRCT
Case 8 (2000; Chan et al.)	73 year/ Female	Deep soft tissue of proximal forearm	Vimentin, SMA, Desmin	CK 8, CK 18	S-100, CD21, CD35, CD68	Surgery	N/A	CIRCT
Case 9 (2000; Chan et al.)	62 year/Male	Mediastinal lymph node	Vimentin	CK 8, CK 18, CK AE 1/AE 3	S-100, CD21, CD35, CD68, SMA, Desmin	Radiotherapy	N/A	CIRCT
Case 10 (2001; Jones et al.)	25 year/ Male	Neck and mediastinal lymph node	Vimentin, CD40, VCAM-1	Negative	S-100, CD45, CD3, CD5, CD20, CD21, CD23, CD35, CNA42, ALK, SMA, Desmin, Keratin cocktail	Surgery, radiotherapy and chemotherapy	NED, 54 months	Reticulum cell sarcoma with mixed dendritic and fibroblastic features
Case 11 (2002; Kakiuchi et al.)	60 year/Male	Retroperitoneal lymph node	Vimentin, SMA	CK 8	S-100, CD1a, CD45, CD21, CD23, CD35, EMA, CD 68	Surgery and radiotherapy	Died after 10 months	CIRCT
Case 12 (2003; Schuerfeld et al.)	66 year/Male	Submandibular lymph node	Vimentin, Desmin, S-100, lysozyme, Ki67 (39 %)	CK AE 1, CK-pool	CD1a, CD3, CD4, CD8, CD20, CD21, CD 45, EMA	Surgery	NED, 1 year	CIRCT
Case 13 (2003; Lucioni et al.)	70 year/Female	Submandibular lymph node	Vimentin, SMA, lysozyme, CD 68	CAM 5.2, CK AE1/AE3	S-100, CD1a, CD45, CD3, CD4, CD5, CD8, CD20, CD21, CD35, EMA, HMB-45	Surgery and chemotherapy	Died after 8 months	CIRCT
Case 14 (2003; Martel et al.)	61 year/Female	Spleen	SMA, CD 68	Negative	S-100, CD45, CD21, CD35, EMA, ALK-1	Surgery	Liver metastases 3.5 years after first excision	FBRCT
Case 15 (2008; Dong et al.)	27 year/Male	Retroperitoneal lymph node	Vimentin, SMA, Lysozyme, Ki67 (10 %)	CK 8, CK 18, CK AE 1/AE 3	S-100, CD1a, CD3, CD20, CD21, CD35, ALK-1, CD 68	Surgery	NED, 13 months	CIRCT
Case 16 (2008; Kwon et al.)	80 year/Female	Cervical lymph node	Vimentin, SMA, CD68, S-100	CK 18, CK AE 1/AE 3	CD21, CD35, Desmin	Surgery	NED, 8 months	CIRCT

Table 1 (continued)

Cases	Age/Sex	Location	Positive immunostaining	Cytokeratin expression	Negative immunostaining	Treatment	Follow up	Diagnosis
Case 17 (2011; Suarez et al.)	71 year/Female	Lymph node of iliac chain	Vimentin, lysozyme, Ki67 (50 %)	CK 18, vCK AE 1/ AE3	S-100, CD14, CD45, CD3, CD4, CD5, CD8, CD20, CD21, CD 23, CD35, EMA, ALK-1, CD 68, SMA, Desmin	Surgery and radiotherapy	N/A	CIRCT
Case 18 (2013; Sundersingh et al.)	64 year/Male	Scalp	Vimentin, SMA CD68, Ki67 (40 %)	CK 8, CK 18	S-100, CD45, CD3, CD20, CD21, CD23, CD35 EMA, ALK-1, HMB-45, CD34, Desmin	Surgery and radiotherapy	Died after 10 months	CIRCT
Case 19 (2013; Sundersingh et al.)	45 year/Female	Breast	Vimentin, SMA Ki67 (80–90 %)	CK 8, CK 18	S-100, CD21, CD23, CD35, ALK-1, Desmin, CD68	Surgery and radiotherapy	Died after 14 months	CIRCT
Present case	64 year/Male	Neck mass with cervical lymph nodes	Vimentin, SMA, CD 68, Ki67 (60 %)	CK AE 1/ AE3	S-100, CD45, CD3, CD20, CD21, CD23, EMA, ALK-1, HMB-45, CD34, Desmin	Lymph node excision biopsy	Died after 1 months	CIRCT

NED no evidence of disease, NA not available

Fig. 1 Sheets of epithelioid cells with vesicular nuclei, prominent nucleoli and abundant cytoplasm along with atypical mitotic figure and lymphocytes in the background (H and E, $\times 400$)

2.2 lac/mm³. All other routine biochemical examinations were within normal limit. Ultrasonography demonstrated large heterogeneous mass with punctuated calcification in right side of neck. Lymphoproliferative lesion was suspected on fine needle aspiration cytology (FNAC) examination and urgent biopsy was suggested to confirm the diagnosis.

Histopathological examination was carried out on formalin-fixed, paraffin-embedded tissue sections prepared from excisional biopsy specimen of the right mid cervical lymph node. Grossly, the resected lymph node measuring 6.0 cm $\times$ 5.0 cm $\times$ 4.5 cm was grayish to tan on the cut surface and uniformly solid in texture. It appeared to have a complete capsule. Histologically, the nodal architecture was almost completely effaced by a neoplastic proliferation that focally infiltrated contiguous soft tissues. A rim of compressed residual normal lymphoid tissue was observed in the subcapsular area. Neoplastic growth mostly consisted of diffuse sheets of medium to large polygonal epithelioid cells having large vesicular nuclei, prominent central eosinophilic nucleoli and abundant eosinophilic cytoplasm with indistinct cell borders resulting in a syncytial appearance (Fig. 1). Scattered multinucleated giant cells with irregular to multilobated, hyperchromatic nuclei and prominent nucleoli were found

Fig. 2 Immunostaining of neoplastic cells with vimentin ($\times 400$)

Fig. 3 Immunostaining of neoplastic cells with SMA (×400)

along with small lymphocytes, plasma cells and granulocytes. No focus of necrosis or hemorrhage was observed. Mitotic figures including atypical mitotic figures were conspicuous in the neoplastic growth (40 mitotic figures/10 high power fields). Some tumour cells displayed apoptotic changes. An 18-Fludeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scan failed to demonstrate any other unknown primary site. A panel of immunohistochemical markers was selected suspecting a primary neoplastic lesion of the lymph node.

Immunostaining was performed by applying the streptavidin–biotin–peroxidase-conjugate method in an automated stainer (Ventana BenchMark XT, Ventana Medical Systems, Rosche) utilizing the manufacturer's protocol with pre-diluted ready-to-use antibodies (Dako, Glostrup, Denmark). Immunohistochemistry revealed diffuse positive reaction of the tumor cells for vimentin (V9) (Fig. 2), smooth muscle actin (1A4) (Fig. 3), CD68 (PG-M1) (Fig. 4) and cytokeratin AE1/AE3 (AE1/AE3) (Fig. 5). The neoplastic cells were negative for S-100 (polyclonal), CD45 (2B11+PD7/26), CD3 (polyclonal), CD20 (L26), CD21 (1 F8), CD23 (DAK-CD23), EMA (E29), ALK-1 (ALK1), HMB-45 (HMB-45), CD34 (QBEnd 10) and desmin (D33). Ki-67 (MIB-1) index was 60 % (Fig. 6). The background lymphocytes displayed the positive staining with CD3 and CD45. Considering the

Fig. 5 Immunostaining of neoplastic cells with cytokeratin AE1/AE3 (×400)

immunohistochemical profile we arrived at the diagnosis of cytokeratin-positive interstitial reticulum cell sarcoma. As the patient died within two weeks of the final diagnosis no follow up data is available with us.

Discussion

CIRC were first described in normal lymph nodes by Franke and Moll in the year 1987. They are indigenous to lymphoid organs, originate from mesenchymal stem cells, express cytokeratin and are considered as a subset of FBRCs. Some of these CIRC coexpress SMA and desmin. They have long, slender cytoplasmic processes extending between lymphocytes and are found in the extrafollicular T cell compartment of lymph nodes in the outer and inner cortex and the medulla, particularly along small blood vessels. They also have been identified in the extrafollicular areas of the spleen and in the tonsils. Ultrastructurally, these cells contain abundant intermediate filaments in the perinuclear cytoplasm and cytoplasmic processes and tonofilament like tight bundles [2, 4]. Gould et al. [5] should be credited for first raising the possibility of the existence of a CIRC tumor.

CIRC sarcomas need to be distinguished from poorly differentiated carcinomas, tumors derived from other accessory

Fig. 4 Immunostaining of neoplastic cells with CD68 (×400)

Fig. 6 Immunostaining of neoplastic cells with Ki67 (×400)

dendritic cells (FDC and IDC sarcomas), myofibroblasts, and malignant mesenchymal tumors (i.e., various sarcomas, sarcomatoid variant of anaplastic large-cell lymphoma and malignant melanoma) as they have no characteristic clinical symptoms or histological features [2, 6]. The lack of awareness of these tumors or their expression of cytokeratin and epithelioid morphology lead to a misdiagnosis of metastatic carcinoma, particularly when they are of nodal origin in patients with known carcinoma [2, 4, 7]. All such histologic mimickers have to be eliminated by combining careful light microscopic analysis with the immunohistochemical and/or ultrastructural data and the clinical details [6, 8].

FBRs including CIRC are immunohistochemically reactive for vimentin, SMA, CD68 and variably for desmin and negative for FDC markers like CD21, CD23, CD35 and KiM4p, IDC and LC marker S-100, lymphoid markers CD45, CD3, CD20 and melanoma marker HMB-45. Further negativity for both desmin and anaplastic lymphoma kinase (ALK) is helpful to exclude an inflammatory myofibroblastic tumor [6, 8, 9]. Most of these immunohistochemical features support the diagnosis of CIRCT in the present tumor with epithelioid cell morphology.

Other than pure FBRs or CIRCTs Jones et al. [10] reported a case of reticulum cell sarcoma with mixed dendritic and fibroblastic features, Kakiuchi et al. [11] described a case of CIRCT with Castleman's disease and Suárez et al. [12] found a case of CIRCT coincidentally with an undifferentiated endometrial stromal sarcoma.

As the role of adjuvant chemotherapy and radiotherapy is not clearly defined surgical excision remains the primary mode of treatment in CIRCTs. Prognosis of CIRC sarcomas is difficult to establish due to its variable biologic behavior and limited number of cases [2]. Hence, it needs further future evaluation to provide comprehensive data on this entity.

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Andriko JW, Kaldjian EP, Tsokos M, Abbondanzo SL, Jaffe ES (1998) Reticulum cell neoplasms of lymph nodes: a clinicopathologic study of 11 cases with recognition of a new subtype derived from fibroblastic reticular cells. *Am J Surg Pathol* 22:1048–1058
2. Sundersingh S, Majhi U, Krishnamurthy A, Velusami SD (2013) Cytokeratin-positive interstitial reticulum cell sarcoma: extranodal presentations mimicking carcinoma. *Indian J Pathol Microbiol* 56: 172–175
3. Dong YC, Wu B, Sheng Z, Wang JD, Zhou HB, Zhou XJ (2008) Cytokeratin-positive interstitial reticulum cell tumors of lymph nodes: a case report and review of literature. *Chin Med J (Engl)* 121:658–663
4. Chan AC, Serrano-Olmo J, Erlandson RA, Rosai J (2000) Cytokeratin-positive malignant tumors with reticulum cell morphology: a subtype of fibroblastic reticulum cell neoplasm? *Am J Surg Pathol* 24:107–116
5. Gould VE, Warren WH, Faber LP, Kuhn C, Franke WW (1990) Malignant cells of epithelial phenotype limited to thoracic lymph nodes. *Eur J Cancer* 26:1121–1126
6. Lucioni M, Boveri E, Rosso R, Benazzo M, Necchi V, Danova M, Incardona P, Franco C, Viglio A, Riboni R, Lazzarino M, Magrini U, Canevari A, Paulli M (2003) Lymph node reticulum cell neoplasm with progression into cytokeratin-positive interstitial reticulum cell (CIRC) sarcoma: a case study. *Histopathology* 43:583–591
7. Schuerfeld K, Lazzi S, De Santi MM, Gozzetti A, Leoncini L, Pileri SA (2003) Cytokeratin-positive interstitial cell neoplasm: a case report and classification issues. *Histopathology* 43:491–494
8. Kwon JE, Yang WI, Kim HK, Kwon KW, Kwon TJ, Choi EC, Lee KG (2009) Cytokeratin-positive interstitial reticulum cell sarcoma: a case report with cytological, immunohistochemical, and ultrastructural findings. *Cytopathology* 20:202–205
9. Martel M, Sarli D, Colecchia M, Coppa J, Romito R, Schiavo M, Mazzaferro V, Rosai J (2003) Fibroblastic reticular cell tumor of the spleen: report of a case and review of the entity. *Hum Pathol* 34:954–957
10. Jones D, Amin M, Ordonez NG, Glassman AB, Hayes KJ, Medeiros LJ (2001) Reticulum cell sarcoma of lymph node with mixed dendritic and fibroblastic features. *Mod Pathol* 14:1059–1067
11. Kakiuchi C, Ishida T, Sato H, Katano H, Ishiko T, Mukai H, Kogi M, Kasuga N, Takeuchi K, Yamane K, Fukayama M, Mori S (2002) Secretion of interleukin-6 and vascular endothelial growth factor by spindle cell sarcoma complicating Castleman's disease (so-called 'vascular neoplasia'). *J Pathol* 197:264–271
12. Suárez D, Izquierdo FM, Méndez JR, Escobar J, Cabeza A, Junco P (2011) Tumor of fibroblastic reticular cells of lymph node coincidental with an undifferentiated endometrial stromal sarcoma. report of a case with distinctive immunophenotype and Kikuchi-like necro-inflammatory response. *APMIS* 119:216–220