Int J Clin Exp Pathol 2013;6(5):926-931
www.ijcep.com /ISSN:1936-2625/IJCEP1303032

Original Article

Diffuse hyperplastic mesothelial cells in multiple lymph nodes: case report with review of the literature

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Received March 15, 2013; Accepted March 30, 2013; Epub April 15, 2013; Published April 30, 2013

Abstract: We report a case of diffuse hyperplastic mesothelial cells in multiple lymph nodes. Microscopically, the lymph nodes had a normal follicular pattern. The lymphatic sinus was extremely expanded, within the sinuses the epithelial-like cells proliferated actively in the form of sheets and clusters. Epithelioid-like cells had eosinophilic cytoplasm, prominent nucleoli and vesicular nuclei. Mitotic figures were rarely observed. These cells were immunopositive for Calretinin, CK5/6, D2-40, MC and Ckpan and immunonegative for S-100, HMB45, MelanA, TTF-1, CDX-2, Villin, ALK, CD30, CD20, CD3, CD1a and CD68. In addition, during a 22 months follow-up period failed to identify any malignant neoplasms, thus confirming the benign nature of these cells. It is the first reported case of diffuse hyperplastic of mesothelial cells mainly in the cervical lymph nodes associated with systemic multiple lymph node involvement. Awareness of this event is important for the pathologist in preventing the misdiagnosis of malignancy.

Keywords: Hyperplastic mesothelial cell, lymph nodes, serous effusions, differential diagnosis

Introduction

The presence of hyperplastic mesothelial cells (HMCs) in lymph nodes is extremely rare, and there is no unified naming convention for it. Adenopathy is more common in the thoracic, abdominal, and pelvic. Occurrence of superficial lymph node enlargement is rare. The presence of multiple diffuse hyperplasia mesothelial cells in the lymph nodes can be easily missed in daily practice and often erroneously diagnosed as malignant. We report a case of diffuse hyperplastic of mesothelial cells mainly in the cervical lymph nodes associated with systemic multiple lymph node involvement. To further understand the essence of such lesions and explore the pathogenesis, clinicopathologic features as well as differential diagnosis by review of the literature.

Case presentation

Clinical information

A 12-year-old man, previously healthy, was admitted to the hospital with a 3-months history of right neck mass gradually enlarged. Physical examination revealed bilateral cervical and axillary adenopathy, maximum diameter from 0.5 cm to 2.0 cm, medium to texture, no tenderness and no abnormal changes in the skin surface. CT venograms revealed thrombosis of the right internal jugular vein. Whole body PET-CT showed bilateral neck, the medial edge of the sternocleidomastoid, the bilateral posterior triangle, the bilateral supraclavicular regions and bilateral axillary, upper mediastinum, around the abdominal aorta with multiple nodules with an increase in FDG metabolism; pelvic fluid was also identified. The patient was diagnosed as having metastatic carcinoma of unknown primary origin and underwent the biopsy of the cervical lymph node.

Pathologic findings

Macroscopic examination showed the maximum diameter of the lymph node ranged from 0.8 cm to 1.0 cm, capsule complete, The cut surface was gray red. Microscopically, the lymph nodes had a normal follicular pattern. The lymphatic sinus were extremely expanded,

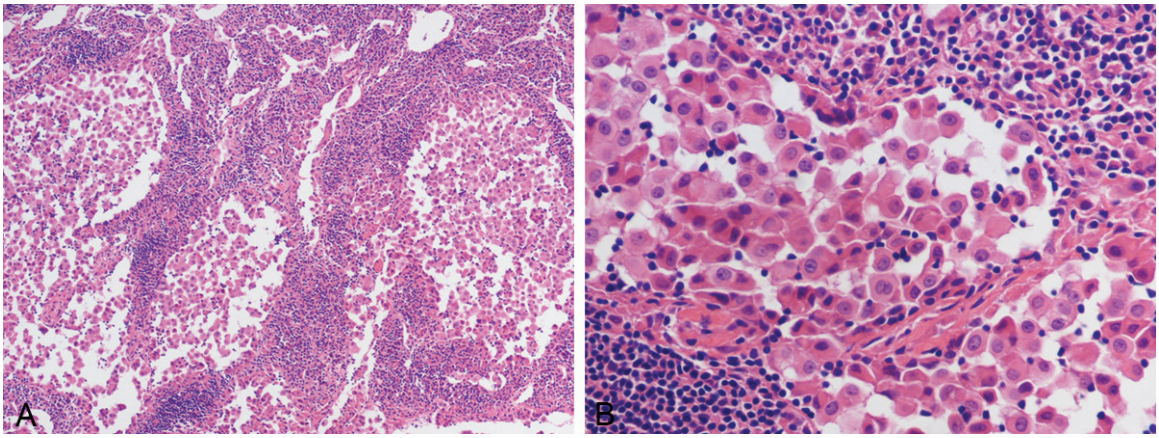

Figure 1. A. Low-power view showing the lymphatic sinus were extremely expanded, within the sinuses the epithelial-like cells proliferated actively in the form of sheets and clusters. (Hematoxylin-eosin, x100). B. High-power view of mesothelial cells. Magnification medullary sinuses were expanded by clusters of round, polygonal mesothelial cells with eosinophilic cytoplasm. These cells showed clear cytoplasm, round or oval nuclei, without nuclear atypia, nucleoli visible. Mitotic figures were rarely observed. (Hematoxylin-eosin, x400).

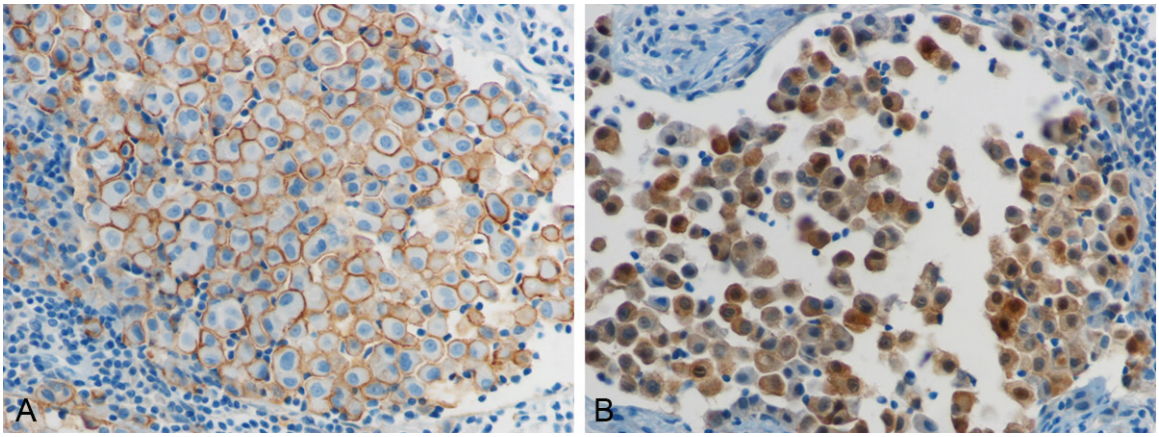

Figure 2. A. Immunohistochemical stain showing mesothelial cells stain positive for D2-40 (×400). B. Mesothelial cells stain positive for MC (×400).

within the sinuses the epithelial-like cells proliferated actively in the form of sheets and clusters. These cells showed no cytologic features of malignancy. Medullary sinuses were expanded by clusters of round, polygonal epithelial cells with eosinophilic cytoplasm, no pleomorphism. These cells showed very poor cell adhesion, clear membrane borders, clear cytoplasm, round or oval nuclei, lightly stained nuclear, without nuclear atypia, nucleoli visible, Mitotic activity was not appreciated. Hyperplastic cells occupy the lymphatic sinus quietly and don't cause damage to surrounding tissue. And there was no stromal reaction (**Figure 1A** and **1B**). All immunohistochemical stains were repeated. The large cells demonstrated strong staining with Calretinin, CK5/6, WT1, Ckpan, EMA, CK7, MC, D2-40 (**Figure 2A** and **2B**). While CK20, TTF-1, CDX-2, Villin, ALK, CD20, CD3, CD30, S-100, HMB45, MelanA, CD1a and CD68 immunohistochemical stains were all negative. The patient was misdiagnosed as metastasis carcinoma, mesothelioma and sinus histiocytosis in different hospitals. A final diagnosis of diffuse hyperplastic mesothelial cells in multiple lymph nodes was rendered eventually. The patient's clinical evaluations during a 22 months period failed to identify any malignant neoplasms, thus confirming the benign nature of these nodal HMCs.

Table 1. Clinical features of previously reported cases with benign mesothelial cells in Lymph Node

Authors	Age/Sex	Effusion	Primary diagnosis	Nodal region	Follow-up
1 Brooks et al. [8]	23/M	Pleura	Infectious syndrome of unknown cause + possible cardiomyopathy	Internal mammary	NED, 3 years
2	52/F	Pleural	Lymphoma	Mediastinal	NED, 10 months
3 Weeks et al. [16]	24 months/F	NM	Wilms' tumor	Renal hilar or periaortic	NM
4	42 months/F	NM	Wilms' tumor	Renal hilar or periaortic	NM
5	47 months/M	NM	Wilms tumor	Renal hilar or periaortic	NM
6	8 months/M	NM	Cystic renal tumors	Renal hilar or periaortic	NM
7 Rutty et al. [17]	23/M	Pleural and pericardial	Lymphoma	Mediastinal	NM
8 Clement et al. [18]	59/F	NM	Ovarian serous borderline tumors	Intraperitoneal	Recent case (when reported)
9	21/F	NM	Sertoli-Leydig cell tumor	Pelvic	Recent case (when reported)
10 Groisman et al. [11]	41/M	Pleura	Pleural Possible tuberculosis + PVP lymphadenopathy	Supraclavicular	NED, 1 year
11 Argani et al. [9]	25/F	Pleura	Hodgkin's disease	Cervical	NED, 2 years
12	32/F	No	Hodgkin's disease	Internal mammary	NED, 8 months
13	38/M	Pleura	Glomerulonephritis + Pneumoconiosis	Hilar	NED, 2 years
14	14/M	Pleura	Takayasu arteritis + CHF	Internal mammary	NED, 2 years
15	48/M	Pleura	Pericarditis	Hilar	
16	61/M	Ascites	Leukemia + valvular disease + CHF	Internal mammary	NED, 1.5 years
17	19/F	Pleural and pericardial	Lymphoma/large cell lymphoma with sclerosis	Mediastinal	NM
18 Cohn et al. [19]	52/F	Ascites	Struma ovarii	Pelvic	NM
19 Parkash et al. [20]	52/F	Pleura	Pericarditis	Mediastinal	Died postopera- tion, 15 days
20	69/F	Pleura	Coronary artery disease	Mediastinal	NED, 2 years
21	70/M	Pleura	Pericarditis	Mediastinal	NED, 6 years
22	55/F	Pleura	Pericarditis	Mediastinal	NED, 3 years
23	68/M	Pericardial	Coronary artery disease pericarditis	Mediastinal	NED, 3 years
24 Isotalo et al. [14]	47/F	Pleural and pericardial	Venous thrombosis	Mediastinal	NED, 6 years
25 Paull et al. [12]	51/F	Pleural	Venous thrombosis	Supraclavicular	NED, 16 months
26 SionVardy et al. [21]	65/M	Pleural	Gastric carcinoma	Subpleural	NED, 2 months
27 Kiret al. [22]	32/F	NM	Ovarian microinvasive serous borderline tumors	Pelvic and abdominal	NM
28 Kim et al. [23]	65/M	NM	Abdominal aortic aneurysm	Mediastinal	NED, 1year
29 Van der et al. [13]	42/F	Ascites	Primary infertility ovarian hyperstimulation syndrome	Cervical	NED, 31 weeks
30 Acikalin et al. [24]	26/F	No	Borderline ovarian mucinous tumors	Pelvic	NED, 18 months
31 Pelosi et al. [25]	74/M	NM	Valvular heart disease	Mediastinal	NM
32 Goyal et al. [10]	16/M	Pleural abdominal cavity	Lymphoma	Neck	NM
33 Moonim et al. [26]	19/F	NM	Chest wall fibromatosis	Axillary	NED, 6 months
34 Colebatch et al. [27]	37/M	pericardial and pleural	acute myocardial infarction	Mediastinal	NM

NM, not mentioned; NED, no evidence of disease; CHF, congestive heart failure; PVP, polyvinylpyrrolidone.

Discussion and review

Benign inclusions in lymph nodes may be glandular. The most well-known intranodal inclusion is typically glandular endometrium [1], parotid gland [2], thyroid [3], breast [4] and pancreas [5], the non-glandular components such as nevus cells [6] and decidual [7] are rare, and mesothelial cells in the lymph nodes is uncommon and under-recognized. The findings of benign mesothelial cells in mediastinal lymph nodes were first described by Brooks et al. in 1990 [8]. To the best of our knowledge, only 34 cases has been reported since (**Table 1**), 16 males and 18 females, the average age at presentation was 39 years (range, 8–74 years). It often occur at one certain site, mesothelial cell inclusions frequently located in the mediastinal lymph node groups [8]. Successively in abdominal, pelvic, renal hilar and periaortic lymph nodes, rarely in superficial lymph nodes (such as the neck, internal mammary and axillary). Only five cases occurrence in the neck [9-13]. We present a case of benign epithelial inclusions within the bilateral cervical lymph nodes associated with axillary, mediastinal and intraperitoneal multiple lymph node involvement. Most of these patients have occurred concurrently with serosal effusions (21/23). 10 cases with tumor, 9 cases with cardiovascular disease, 2 cases with secondary venous thrombosis [12, 14]. In all cases, no evidence of a primary malignant mesothelioma was identified. From the literature, HMCs usually associated with either inflammation, infection, mechanical causes or tumour. A feature common to most of the reported cases was a background of chronic mesothelial irritation caused by inflammatory or neoplastic process. Mesothelial cells gain access to the lymph nodes through the expansion lymphatic channels [8]. Mesothelial cells are thought to be transported to the lymph nodes through lymphatics system, thus there were mesothelial cell clusters identified within nodal lymphatics [14]. The present case of HMCs within mediastinal lymph nodes had pelvic effusion secondary to venous thrombosis, which was similar to the previously described cases. Mesothelial reactions are thought to disrupt mesothelial stomata, allowing dislodged mesothelial cells access to sub-mesothelial lymphatics, lead to presence of the clusters of mesothelial cells in the lymph nodes.

The histopathological of HMCs need immunohistochemistry and ultrastructural studies to confirm mesothelial cell origin. Mesothelial markers contain Calretinin, HBME-1 and D2-40, electron microscopy illustrating the slender microvilli characteristic of mesothelial cells. HMCs can be easily misdiagnosed histologically for metastatic carcinoma and malignant mesothelioma; it often poses a serious diagnostic dilemma to the pathologists. The present case misdiagnosed as metastatic carcinoma or malignant mesothelioma at the beginning, however, malignancy primary tumor was not found during the follow-up period. These repeatedly immunohistochemical and follow-up confirmed the diagnosis to diffuse hyperplasia of mesothelial cells in lymph nodes. Review of the literature, most of the patients was misdiagnosed initially as malignant lesions and received radiotherapy and chemotherapy, and finally combined with long-term follow-up and the clinical history to correct diagnosis of benign HMCs in the node sinuses. Follow-up ranged from 31 weeks to 6 years in 19 patients, no lesions showed evidence of malignancy.

With the high incidence of serous effusions in the general, nodal HMCs are probably not rare but are likely under recognized. Awareness of this event is important for the pathologist in preventing the misdiagnosis of malignancy. The serious problem posed by these inclusions is distinction from lesions of lymph nodes sinuses. (1) Metastasis carcinoma: high incidence in the older patients and often with a definite primary lesion, good adhesion between cells, nested or irregular glandular structure, cellular atypia, mitotic activity, specific immune markers for suggesting tissue origin are positive. Mesothelial cells also express epithelial markers, so a combination of multiple markers for the differential diagnosis is needed. (2) Anaplastic large cell lymphoma: cells either scattered or clustered, nuclear atypia and high mitotic activity, express CD30 and ALK as well as T and B lymphocytes markers, some express epithelial markers. (3) Metastatic malignant melanoma: the majority has an antecedent history of melanoma (skin and mucous membrane), morphology diversity, lipofuscin granules can be seen in the cytoplasm. Malignant melanoma often has diffuse positivity for S-100 protein as well as possible positivity for melanocytic markers, including HMB45, MelanA. (4) Sinus histiocytosis: large histiocytic cells, abundant cytoplasm, cell morphology mild, lacked atypia, were positive for CD68, S-100 and were

negative for epithelial and mesothelial markers. (5) Metastatic malignant mesothelioma: often with a definite primary lesion, serosal surface blockbuster fusion of nodules, with high-grade atypia, with formation of nipple and microtubules, convinced destructive stromal infiltrates and invasion was necessary to confirm the diagnosis of malignant. The homozygous deletion of p16 detected by FISH was a reliable way to distinguish the benign/reactive and malignant mesothelial proliferations. The majority of mesothelioma cases were positive for the p16 gene deletion, whereas none of the benign/reactive cases were positive the deletion [15].

To our knowledge, diffuse hyperplasia of mesothelial cells in lymph multiple nodes have never been described. The potential problem of misdiagnosis as mesothelioma can be avoided by an awareness of these conclusions, supported by clinical course and immunohistochemical results. Over 22-months follow-up period, the patient is free of disease. However, we wonder whether such diffuse proliferative mesothelial cells will last 'static, benign'. Careful clinical follow-up and many more cases are required for depth of investigation.

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References

[1] Javert CT. The spread of benign and malignant endometrium in the lymphatic system with a note on coexisting vascular involvement. Am J Obstet Gynecol 1952; 64: 780-806.

[2] Brown RB, Gaillard RA and Turner JA. The significance of aberrant or heterotopic parotid gland tissue in lymph nodes. Ann Surg 1953; 138: 850-856.

[3] Meyer JS and Steinberg LS. Microscopically benign thyroid follicles in cervical lymph nodes. Serial section study of lymph node inclusions and entire thyroid gland in 5 cases. Cancer 1969; 24: 302-311.

[4] Turner DR and Millis RR. Breast tissue inclusions in axillary lymph nodes. Histopathology 1980; 4: 631-636.

[5] Murayama H, Kikuchi M, Imai T, Yamamoto Y and Iwata Y. A case of heterotopic pancreas in lymph node. Virchows Arch A Pathol Anat Histol 1978; 377: 175-179.

[6] Epstein JI, Erlandson RA and Rosen PP. Nodal blue nevi. A study of three cases. Am J Surg Pathol 1984; 8: 907-915.

[7] Burnett RA and Millan D. Decidual change in pelvic lymph nodes: a source of possible diagnostic error. Histopathology 1986; 10: 1089-1092.

[8] Brooks JS, LiVolsi VA and Pietra GG. Mesothelial cell inclusions in mediastinal lymph nodes mimicking metastatic carcinoma. Am J Clin Pathol 1990; 93: 741-748.

[9] Argani P and Rosai J. Hyperplastic mesothelial cells in lymph nodes: report of six cases of a benign process that can stimulate metastatic involvement by mesothelioma or carcinoma. Hum Pathol 1998; 29: 339-346.

[10] Goyal M, Kodandapani S, Sharanabasappa SN and Palanki SD. Mesothelial cell inclusions mimicking adenocarcinoma in cervical lymph nodes in association with chylous effusion. Indian J Med Paediatr Oncol 2010; 31: 62-64.

[11] Groisman GM, Amar M, Weiner P and Zamir D. Mucicarminophilic histiocytosis (benign signet-ring cells) and hyperplastic mesothelial cells: two mimics of metastatic carcinoma within a single lymph node. Arch Pathol Lab Med 1998; 122: 282-284.

[12] Paull G and Mosunjac M. Fine-needle aspiration biopsy and intraoperative cytologic smear findings in a case of benign mesothelial-cell inclusions involving a lymph node: case report and review of the literature. Diagn Cytopathol 2003; 29: 163-166.

[13] van der Weiden RM, Meijers CJ and Hegt VN. Ectopic mesothelial cell proliferation in cervical lymph nodes after severe ovarian hyperstimulation syndrome. Fertil Steril 2005; 83: 739-741.

[14] Isotalo PA, Veinot JP and Jabi M. Hyperplastic mesothelial cells in mediastinal lymph node sinuses with extranodal lymphatic involvement. Arch Pathol Lab Med 2000; 124: 609-613.

[15] Monaco SE, Shuai Y, Bansal M, Krasinskas AM and Dacic S. The diagnostic utility of p16 FISH and GLUT-1 immunohistochemical analysis in mesothelial proliferations. Am J Clin Pathol 2011; 135: 619-627.

[16] Weeks DA, Beckwith JB and Mierau GW. Benign nodal lesions mimicking metastases from pediatric renal neoplasms: a report of the National Wilms' Tumor Study Pathology Center. Hum Pathol 1990; 21: 1239-1244.

[17] Rutty GN and Lauder I. Mesothelial cell inclusions within mediastinal lymph nodes. Histopathology 1994; 25: 483-487.

[18] Clement PB, Young RH, Oliva E, Sumner HW and Scully RE. Hyperplastic mesothelial cells within abdominal lymph nodes: mimic of meta-

static ovarian carcinoma and serous borderline tumor--a report of two cases associated with ovarian neoplasms. Mod Pathol 1996; 9: 879-886.
[19] Cohn DE, Folpe AL, Gown AM and Goff BA. Mesothelial pelvic lymph node inclusions mimicking metastatic thyroid carcinoma. Gynecol Oncol 1998; 68: 210-213.
[20] Parkash V, Vidwans M and Carter D. Benign mesothelial cells in mediastinal lymph nodes. Am J Surg Pathol 1999; 23: 1264-1269.
[21] Sion-Vardy N, Diomin V and Benharroch D. Hyperplastic mesothelial cells in subpleural lymph nodes mimicking metastatic carcinoma. Ann Diagn Pathol 2004; 8: 373-374.
[22] Kir G, Eren S and Kir M. Hyperplastic mesothelial cells in pelvic and abdominal lymph node sinuses mimicking metastatic ovarian microinvasive serous borderline tumor. Eur J Gynaecol Oncol 2004; 25: 236-238.
[23] Kim YM, Kim KR and Ro JY. Mesothelial Cell Inclusions Mimicking Metastatic Carcinoma in Mediastinal Lymph Node: A Case Report. Korean J Pathol 2004; 38: 46-49.
[24] Acikalin MF, Ozalp S and Turan D. Mesothelial pelvic lymph node inclusion in a patient with ovarian microinvasive borderline mucinous tumor: case report with review of the literature. Int J Gynecol Cancer 2007; 17: 917-921.
[25] Pelosi G, Sonzogni A and Rosai J. Images in pathology. Benign hyperplastic mesothelial cells in lymph node. Int J Surg Pathol 2007; 15: 297-299.
[26] Moonim MT, Ng WW and Routledge T. Benign metastasizing mesothelial cells: a potential pitfall in mediastinal lymph nodes. J Clin Oncol 2011; 29: e546-548.
[27] Colebatch A, Clarkson A and Gill AJ. Benign mesothelial cells as confounders when cytokeratin immunohistochemistry is used in sentinel lymph nodes. Hum Pathol 2011; 42: 1209-1210; author reply 1210-1201.