Int J Clin Exp Pathol 2017;10(8):8751-8755
www.ijcep.com /ISSN:1936-2625/IJCEP0058279

Case Report

Lymphangiosarcoma of the jejunum in a 44-year-old man: report of a case and review of literature

Jinping Hou[1], Huali Wang[1], Haijing Liu[2], Hongwei Guan[1], Qiuping Zhang[1], Wenjing Qi[1], Dan Chen[1], Chang Shi[1]

[1]Department of Pathology, Dalian Medical University First Hospital, Dalian, Liaoning, China; [2]Department of Pathology, Health Science Center of Peking University, Beijing, China

Received May 26, 2017; Accepted May 27, 2017; Epub August 1, 2017; Published August 15, 2017

Abstract: Lymphangiosarcoma is a malignant tumor arising from lymphatic endothelial cells and has largely been abandoned in the current classification of endothelial neoplasms. Recently, lymphangiosarcoma has been resurrected by several novel markers for lymphatic endothelium available for immunohistochemistry. Here, we reported a new case of lymphangiosarcoma that was located in the Jejunum of a 44-year-old man. To our best knowledge, this is the first report of lymphangiosarcoma in small intestine with no known history of lymphedema, lymphaticmalformation or previous radiation.

Keywords: Lymphangiosarcoma, D2-40, Prox-1, VEGFR-3

Introduction

Lymphangiosarcoma (LAS), by definition, arises from lymphatic endothelial cells and has largely been abandoned in the current classification of endothelial neoplasms. The concept of lymphangiosarcoma was firstly raised in 1948 by Stewart and Treves [1]. Since then it has been used to describe a rare malignant tumor that is most frequently associated with postmastectomy lymphedema known as Stewart-Treves syndrome, or that arises in patients with long-term congenital hereditary and non-hereditary lymphedema, radiation exposure or lymphaticmalformation [2]. However, recent studies showed that this malignancy was not derived from lymphatic vessels, but from vascular endothelial cells [3]. Therefore, use of the term "lymphangiosarcoma" for lymphedema associated malignant tumor could be a misnomer and "hemangiosarcoma (AS)" might be more appropriate. Actually, morphologic diagnosis of LAS from AS is particularly difficult even for experienced pathologists because of the close histologic and embryogenetic relationship between the two types of sarcomas. Besides, lymphatic differentiation is common in AS. Therefore, Enzinger and Weiss summarized that "Since it is usually impossible to determine which tumors display lymphatic versus vascular differentiation, all are referred to as angiosarcoma, even those that arise in the setting of lymphedema" [4]. Only recently, however, lymphangiosarcoma has been resurrected by several novel selective markers for lymphatic endothelium available for immunohistochemistry, including D2-40, Prox-1 and VEGFR-3 [5]. Here we reported a new case of lymphangiosarcoma located in the Jejunum.

Case report

A 44-year-old man with a history of smoking 20 cigarettes a day on average for 17 years was the subject of this report. This patient firstly showed intermittent moderate pains around umbilicus in 2011 under no obvious inducement, without radiating pain, nausea or vomiting. However, colonoscopy examination was normal. In April 2012, he presented to our institution with recurrence of abdominal pains accompanied with nausea and vomiting. After preliminary diagnosis of intestinal obstruction, he was improved with corresponding therapies and was discharged. However, two years later on March 21, 2014, the patient presented again with progressive and insufferable abdominal pains without nausea or vomiting. Physical

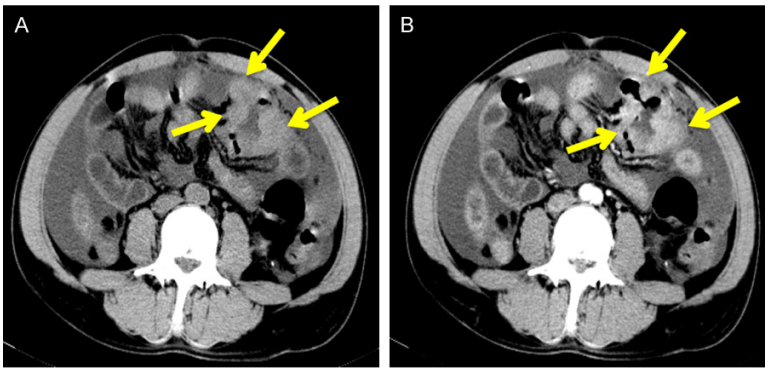

Figure 1. The small intestine lesion on computed tomography (CT). A. Asymmetric thickening of small intestine wall on plain CT image (arrows). B. Dynamic contrast CT showed markedly enhancement of small intestine wall (arrows).

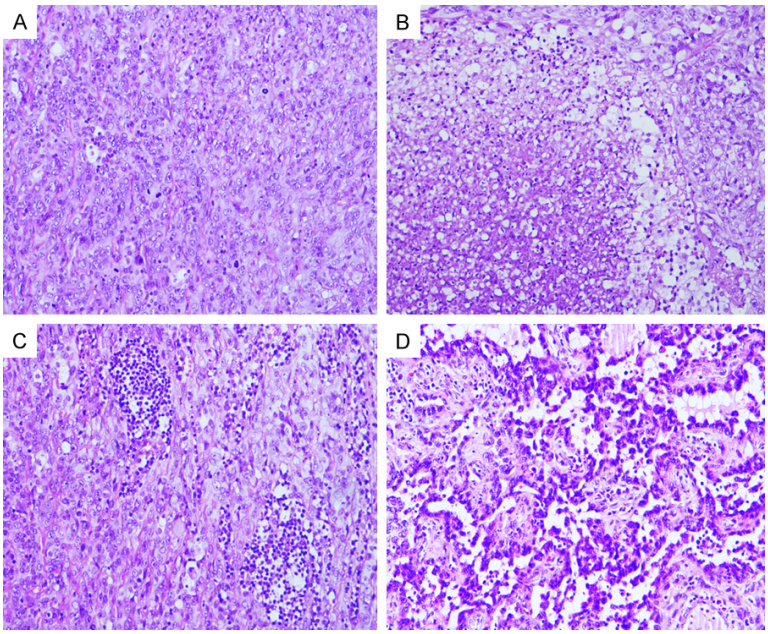

Figure 2. The light microscopy examination of the sarcoma. A-C. The poorly-differentiated areas; A. The tumor was composed predominantly of atypical epithelioid cells arranged in solid areas, with five to six mitotic figures per high-power field; B. Tumorous necrosis could be observed; C. Lymphocytic infiltrates were prominent. D. The well-differentiated areas. The tumor was composed of irregular interanastomosing channels largely devoid of red blood cells, but with proteinaceous fluid or lymphocytes.

and colonoscopy examination showed nothing abnormal, whereas enhanced abdominal computed tomography (CT) showed obvious thickening of focal small bowel wall (**Figure 1**). Therefore, the patient had a surgical operation. Serous ascites was observed during the operation. Ascites analysis revealed nothing abnormal in the protein, specific gravity, total cell numbers, neutrophil, lymphocyte, nucleated cells and mesothelial cells.

A segment of Jejunum containing the lesion was removed. For naked eye examination, there was an ulcerative lesion of 9×3.5 cm^2 in the mucosa of the Jejunum. The lesion with moderate texture had infiltrated into the serous membrane. The small intestinal wall was thickened. There were several ascaris lumbricoides in the lumen. For light microscopy examination, tumor tissues were fixed in 4% neutral-buffered formaldehyde solution (pH 7.0) and were routinely processed for paraffin embedding. Sections of 4 μm thickness were stained with hematoxylin and eosin. Histologic examination revealed a nonencapsulated tumor that had infiltrated from the intestinal mucosa to the serous membrane. This tumor was composed predominantly of atypical epithelioid cells arranged in solid areas, which was considered to be poorly differentiated (**Figure 2A-C**). The epithelioid cells had irregular round or oval nuclei with prominent nucleoli, abundant cytoplasm and indistinct cell borders (**Figure 2A**). Five to six mitotic figures per high-power field were observed (**Figure 2A**). Tumorous necrosis (**Figure 2B**) could be seen, and lymphocytic infiltrates (**Figure 2C**) were prominent. In some areas considered as well-differentiated, the tumor was composed of irregular interanastomosing channels largely devoid of red blood cells, but with proteinaceous fluid and, occasionally, lymphocytes. These channels were lined by hobnail endothelial cells characterized by cuboidal cells with scant cytoplasm and apical nuclei protruding into the lumen (**Figure 2D**).

On immunohistochemistry, the tumor cells were reactive strongly and diffusely to D2-40 (anti-podoplanin) (**Figure 3A**) and Prox-1 (pros-

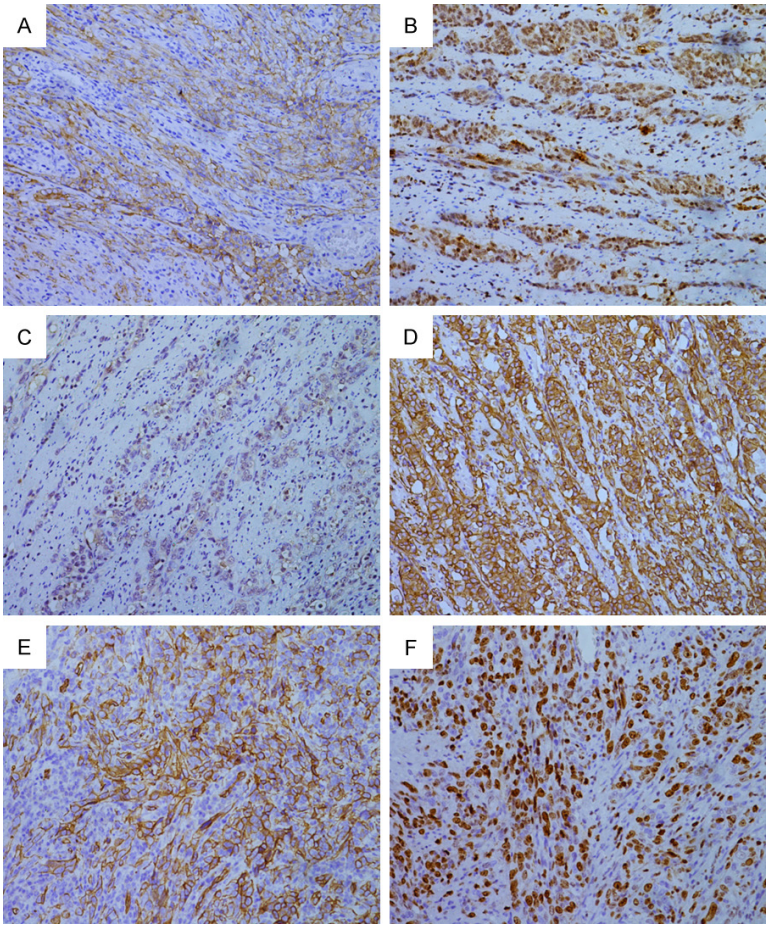

Figure 3. Different expressions of D2-40 (A), Prox-1 (B), VEGFR-3 (C), CD31 (D), CD34 (E) and Ki-67 (F) in the sarcoma.

pero-related homeobox 1), (**Figure 3B**) but weakly and diffusely to VEGFR-3 (vascular endothelial growth factor receptor-3) (**Figure 3C**). In addition, the tumor cells were also positive strongly and diffusely for endothelial markers CD31 (**Figure 3D**), focally for CD34 (**Figure 3E**), but negative for pan-cytokeratin, CK20, CK5/6, EMA (epithelial membrane antigen), SMA (smooth muscle actin), actin, calretinin, mesothelin, CD21, LCA or S-100. Ki-67 immunohistochemical staining demonstrated a proliferative index of 60% in the neoplastic lymphatic endothelial cells (**Figure 3F**). On the basis of clinical, histologic, immunohistochemical findings, a final diagnosis of vascular sarcoma with prominent lymphatic differentiation, lymphangiosarcoma (LAS), was made.

Discussion

Lymphangiosarcoma is an extremely rare malignant tumor in humans arising from the lymphatic endothelial cells of the lymph vessel. Morphologic diagnosis of lymphangiosarcomas from hemangiosarcoma is usually impossible, so pathologists have used the term hemangiosarcoma to encompass both of them for many years. Only recently, antigens preferentially expressed by lymphatic endothelial cells including D2-40, Prox-1 and VEGFR-3 have been discovered, which allow lymphangiosarcomas to be defined pathologically.

D2-40 is a monoclonal antibody that reacts with an oncofetal membrane antigen known as the M2A antigen [6], which is present in fetal germ cells of the testis as well as lymphatic endothelial cells selectively [7, 8]. Because of its high sensitivity and specificity for lymphatic endothelium, D2-40 can be used in a routine diagnostic pathology examination to evaluate whether a particular tumor growth involves the lymphatic systems [9].

Prox-1 is a nuclear transcription factor that plays a major role during embryonic development, including differentiation of the lymphatic vasculature [10, 11]. Therefore, it is considered as a specific and sensitive lymphatic marker [12]. Further studies suggested Prox-1 could be used as a nuclear lymphatic marker in conjunction with other cytoplasmic antibodies for identifying lymphatic differentiation in vascular neoplasms.

VEGFR-3 is another marker of lymphatic endothelium. Genetic studies have demonstrated that VEGFR-3 plays essential roles in endothelial cells during developmental lymphangiogenesis. It is the receptor for VEGFC, a cytokine important for the growth and differentiation of lymphatic endothelium. VEGFR-3 expression is switched on during blood to lymphatic endothelial cell differentiation, and this process is known to require Prox-1 during development [13].

Studies showed that all the three markers are expressed in lymphatics of normal adult tissues, whereas blood vessels usually express none of them [5]. So, they appear to be rather specific markers of lymphatic neoplasms [5]. Kahn et al concluded that a subset of hemangiosarcomas can undergo at least partial differentiation along the lymphatic endothelial lineage and could be classified as lymphangiosarcomas [8]. In 2011, Yu etc. reported the first true lymphangiosarcoma of the vocal cord defined by D2-40 immunohistochemistry and ultrastructural study [14].

A diagnosis of lymphangiosarcoma is commonly based on the history, clinical signs, histopathological lesions and biological behavior of the tumor. In this patient described in the present report, the tumor cells were reactive strongly and diffusely to D2-40, Prox-1 and CD31, weakly and diffusely to VEGFR-3, and focally to CD34. Combined with the clinical signs and histological characteristics, a diagnosis of lymphangiosarcoma could be made. After operation, the patient did not receive any adjunctive therapy and died 8 months later at home, indicating the lethal prognosis of this disease.

Lymphangiosarcomas are now treated with a multimodal approaches. Complete initial surgical resection is preferred treatment and radiation is used as adjunctive treatment together with surgery or chemotherapy [15]. To date, it is not clear whether separating LAS from AS is clinically important and there are no specific therapies directed to LAS. But it is conceivable that reinstituting the term lymphangiosarcoma may provide more options for targeted therapy in the future.

In conclusion, this report described a 44-year-old man with a history of repeated abdominal pains who was diagnosed as lymphangiosarcoma after operation. The distinct morphology and the expressions of the lymphatic endothelial markers D2-40, Prox-1 and VEGFR-3 as well as serous ascites observed in the operation provide strong evidence that this neoplasm could be of lymphatic origin rather than of blood vessel origin. To our best knowledge, this is the first report of lymphangiosarcoma arising in small intestine with no known history of lymphedema, lymphatic malformation or previous radiation.

Acknowledgements

We thank Dr. Bu-Lang Gao (Shijiazhuang First Hospital, Hebei Medical University) for editing the English language.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Chang Shi, Department of Pathology, Dalian Medical University First Hospital, 222 Zhongshan Road, Xigang District, Dalian 116011, Liaoning, China. Tel: 86-411-83635963-3253; Fax: 86-411-83635963-3253; E-mail: scdoctor@126.com

References

[1] Stewart FW, Treves N. Lymphangiosarcoma in postmastectomy lymphedema: a report of six cases in elephantiasis chirurgica. Cancer 1948; 1: 64-81.

[2] Kerchner K, Fleischer A, Yosipovitch G. Lower extremity lymphedema update: pathophysiology, diagnosis, and treatment guidelines. J Am Acad Dermatol 2008; 59: 324-331.

[3] McWilliam LJ, Harris M. Histogenesis of postmastectomy angiosarcoma--an ultrastructural study. Histopathology 1985; 9: 331-343.

[4] Enzinger JR, Weiss SW. Enzinger and Weiss's soft tissue tumors. 5 edition. Philadelphia, PA: Mosby; 2007. pp. 703-718.

[5] Mankey CC, McHugh JB, Thomas DG, Lucas DR. Can lymphangiosarcoma be resurrected? A clinicopathological and immunohistochemical study of lymphatic differentiation in 49 angiosarcomas. Histopathology 2010; 56: 364-371.

[6] Marks A, Sutherland D, Bailey D. Characterization and distribution of an oncofetal antigen (M2A antigen) expressed on testicular germ cell tumours. Br J Cancer 1999; 80: 569-578.

[7] Sonne SB, Herlihy AS, Hoei-Hansen CE. Identity of M2A (D2-40) antigen and gp36 (Aggrus, T1A-2, podoplanin) in human developing testis, testicular carcinoma in situ and germ-cell tumours. Virchows Arch 2006; 449: 200-206.

[8] Kahn HJ, Bailey D, Marks A. Monoclonal antibody D2-40, a new marker of lymphatic endothelium, reacts with Kaposi's sarcoma and a subset of angiosarcomas. Mod Pathol 2002; 15: 434-440.

[9] Kahn HJ, Marks A. A new monoclonal antibody, D2-40, for detection of lymphatic invasion in primary tumors. Lab Invest 2002; 82: 1255-1257.

[10] Lavado A, Oliver G. Prox1 expression patterns in the developing and adult murine brain. Dev Dyn 2007; 236: 518-524.
[11] Procino A. Overexpression of Prox-1 gene in omental adipose tissue and adipocytes compared with subcutaneous adipose tissue and adipocytes in healthy patients. Cell Biol Int 2014; 38: 888-891.
[12] Wigle JT, Harvey N, Detmar M. An essential role for Prox1 in the induction of the lymphatic endothelial cell phenotype. EMBO J 2002; 21: 1505-1513.
[13] Gutierrez KD, Morris VA, Wu D, Barcy S, Lagunoff M. Ets-1 is required for the activation of VEGFR-3 during latent Kaposi's sarcoma-associated herpesvirus infection of endothelial cells. J Virol 2013; 87: 6758-6768.
[14] Yu L, Yang SJ. Lymphangiosarcoma of the vocal cord: a rare entity defined by a D2-40 immunohistochemical and ultrastructural study. J Clin Oncol 2011; 29: e57-61.
[15] Quarmyne MO, Gupta A, Adams DM. Lymphangiosarcoma of the thorax and thoracic vertebrae in a 16-year-old girl. J Clin Oncol 2012; 30: e294-298.