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Letter to the Editor

Benign mesothelial nodules reflux within acquired cutaneous lymphangiectasia associated with huge ovarian clear cell carcinoma

To the Editor:

There have been some interesting reports describing a unique case of benign mesothelial nodule reflux (BMNR) in the cutaneous lymph vessels (the benign mesothelial nodules are composed of polygonal mesothelial cells admixed with a variable number of inflammatory cells, especially the histiocytes) including: (i) 'Embolization of mesothelial cells' in lymphatics of a 60-year-old male on the abdominal skin with hernia, accompanied by alcoholic cirrhosis and severe ascites;[1] (ii) 'Mesothelial cells reflux' within acquired cutaneous lymphangiectasia of a 56-year-old male on the abdominal skin, accompanied by hepatitis C virus-induced cirrhosis and severe ascites;[2] and (iii) 'Benign mesothelial nodules' in lymphatics of a 55-year-old female on the umbilical skin with huge hernia, associated with massive ovarian fibroma.[3] Although mesothelial cell inclusions within the mediastinal or abdominal lymph nodes are a well known phenomenon,[1,4] BMNR in the cutaneous lymphatics is rarely reported and potentially represents a new morphological and clinicopathological entity. To the best of our knowledge, BMNR was first described as the lymphatic dissemination and embolization of mesothelial cells by Rossi Suárez-Viela and Izquierdo-Garcia in the late 1990s,[1] and to date, only four cases of BMNR (including our own) have been reported in the English literature.[1–3] BMNR in the cutaneous lymph vessels is an extremely uncommon and unestablished entity; however, we should be aware that pathologists might misinterpret BMNR as the lymphatic dissemination of malignant cells. We showed the first case of BMNR within acquired cutaneous lymphangiectasia, which was associated with huge ovarian clear cell carcinoma and ascites in an obese patient.

The patient, who was a woman in her late forties with marked obesity (BMI: 45 kg/m^2) and an unremarkable previous medical history, presented with abnormal vaginal/uterine bleeding due to a huge ovarian carcinoma, accompanied by a subsequent and diffuse erythema with local heat. The erythema was approximately 25 cm in diameter and covered the whole abdominal skin (Fig. 1a). Dermatologists first interpreted it as cellulitis, and antibiotics were administered but were not effective. Scanning magnification of a biopsy specimen of the umbilical lesion (Fig. 1b) revealed that the deep dermis and superficial subcutis demonstrated a collection of variably dilated lymphatic vessels; microscopy revealed a mildly thickened wall; the endothelium was positive for D2-40 and CD31, and was frequently filled with small glomeruloid nodules (Fig. 1c). On a high-power view, the cellular nodules consisted of a substantial number of CD68-positive histiocytes and siderophages, admixed with lymphocytes/neutrophils, CD31-positive microvessels and α-SMA-positive myofibroblast-like cells The nodules were characteristically lined by medium-sized to large polygonal or cuboidal epithelioid cells (Fig. 1c). These lining cells contained relatively abundant eosinophilic cytoplasm and likely centrally-located nuclei (Fig. 1c), and were immunohistochemically positive for calretinin (Fig. 1d), D2-40, WT1 and cytokeratins (AE1/AE3 and CK5/6) and negative for IMP3, GLUT1, HNF-1β and Napsin A. In addition, the deletion of p16 or BAP1 was not detected by fluorescence *in situ* hybridization (FISH) testing or immunohistochemistry, respectively. Based on all of these features, we concluded that the lining epithelioid cells were benign mesothelial cells. In contrast, on gross examination, the cut surface of the ovarian multilocular tumor showed a solid firm and lobulated mass, measuring more than $30 \times 18 \times 13$ cm in size, which appeared yellow-whitish to gray-whitish in color, accompanied by focal necrosis and hemorrhage. The typical microscopic findings (Fig. 1e) included a proliferation of medium-sized to large highly atypical epithelial cells with hyperchromatic pleomorphic nuclei and abundant clear to eosinophilic cytoplasm, arranged in a predominantly papillary/micropapillary or microcystic growth fashion that frequently shows a hobnail appearance. Those carcinoma cells were immunohistochemically positive for HNF-1β and Napsin A. Neither distant metastasis nor the peritoneal dissemination of clear cell carcinoma were observed. A gross examination revealed light hemorrhagic ascites, while a histopathological examination revealed numerous inflammatory foci on the surface of omentum, very similar to the abovementioned small intralymphatic glomeruloid nodules, consisting of granulation-like tissue, lined by variably hyperplastic mesothelial cells without any atypia (Fig. 1f). We ultimately made a diagnosis of cutaneous BMNR within acquired lymphangiectasia due to the peritoneal mesothelial and inflammatory nodule drainage, which was potentially induced by the gradient of abdominal pressure secondary to huge ovarian clear cell carcinoma and ascites. To date, the patient has been followed for approximately one year since surgery, and remains well without any sign of recurrence.

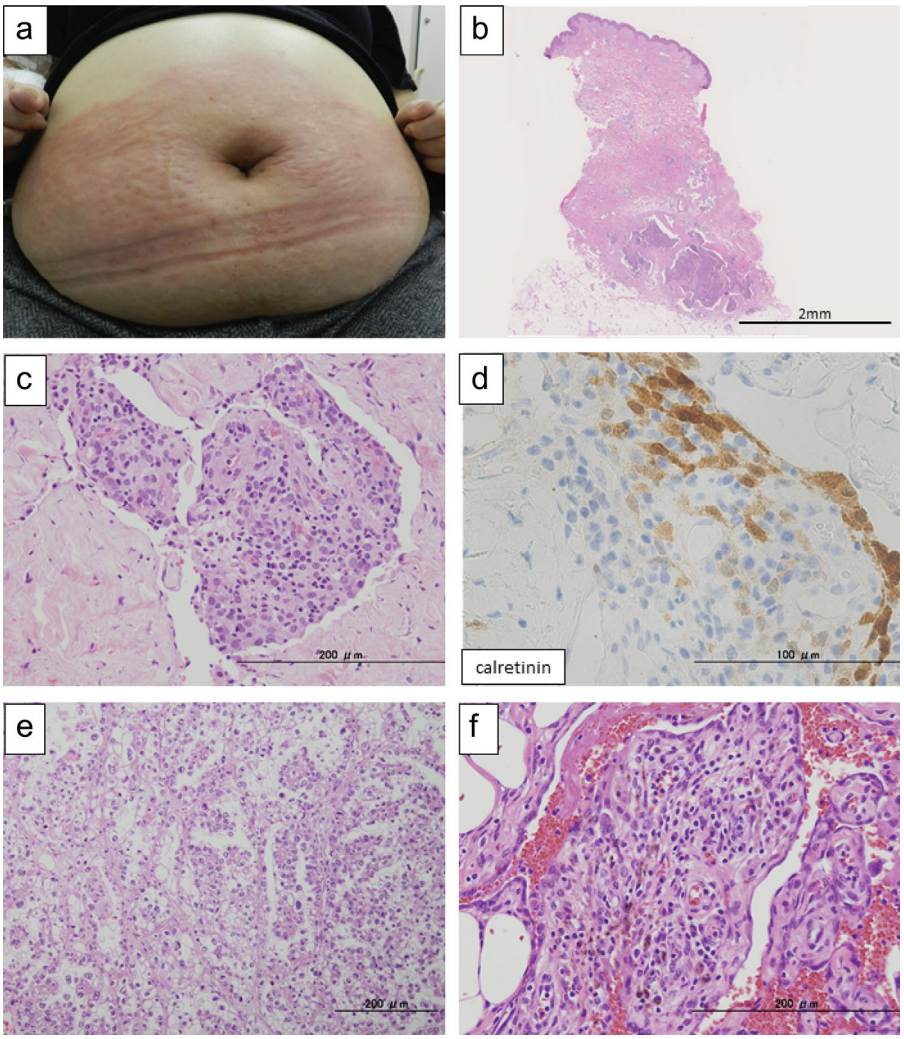

Figure 1 Gross, microscopic and immunohistochemical examinations of the cutaneous lymphatic BMNR specimen. (**a**) The clinical findings: the markedly obese patient showed a subsequent and diffuse erythema with local heat. The erythema was approximately 25 cm in diameter and was located on the abdominal skin. (**b**) Scanning magnification of the umbilical lymphatic BMNR biopsy specimen (H&E staining) showed that the deep dermis and superficial subcutis had a collection of variably dilated lymphatic vessels; microscopy revealed a mildly thickened wall and a lining of bland endothelial cells; the lining was frequently filled with small glomeruloid cellular nodules. Bar = 2 mm. (c) A high-power view (H&E staining) revealed that the cellular nodules consisted of a substantial number of histiocytes and siderophages, admixed with lymphocytes/neutrophils, microvessels, and myofibroblast-like cells, characteristically lined by medium-sized to large polygonal or cuboidal epithelioid mesothelial cells. These lining mesothelial cells contained relatively abundant eosinophilic cytoplasm and likely centrally-located nuclei. Bar = 200 μm. (**d**) The immunohistochemistry findings: the lining polygonal to cuboidal cells were specifically positive for calretinin. Bar = 100 μm. (**e**) In contrast, the huge ovarian multilocular tumor microscopically (H&E staining) showed the proliferation of medium to large sized highly atypical epithelial cells with hyperchromatic pleomorphic nuclei and abundant clear to eosinophilic cytoplasm; the manner of growth was predominantly papillary/micropapillary or microcystic growth fashion, and a hobnail appearance was frequently observed. Bar = 200 μm. (**f**) Microscopy revealed that the surface omentum (H&E staining) contained numerous inflammatory foci, very similar to the abovementioned intralymphatic small glomeruloid nodules (i.e., BMNR), consisting of granulation-like tissue, lined by variably hyperplastic mesothelial cells without any atypia. We ultimately made a diagnosis of cutaneous BMNR within acquired lymphangiectasia due to the drainage of the peritoneal mesothelial and inflammatory nodules, which was potentially induced by the gradient of abdominal pressure, which occurred secondarily to huge ovarian clear cell carcinoma. Bar = 200 μm.

The most critical differential diagnosis in the present case of cutaneous lymphatic BMNR with lymphatic invasion of ovarian clear cell carcinoma. Our case showed no local invasion, metastasis or peritoneal dissemination, and the cells comprising the intralymphatic glomeruloid nodules displayed much lower cellular/structural atypia in comparison to ovarian carcinoma; thus, it was easy to clinicopathologically and immunohistochemically distinguish from the possibility of extensively spreading carcinoma cells. Besides, we agree with previous studies, which indicate the

importance of applying a wide panel of immunohistochemical antibodies in order to make a conclusive diagnosis of BMNR in the cutaneous lymphatics.[1–3] In addition to testing the submitted specimen for mesothelial markers, further analyses, including FISH and other immunochemical analyses would be powerful supplementary tools for excluding the possibility of malignancy, including malignant mesothelioma.[5] In contrast, the benign to low-grade malignant tumor histologies that should be included in the differential diagnoses of the current case include intravascular/intralymphatic histiocytosis, intravascular/intralymphatic papillary endothelial hyperplasia, reactive angioendotheliomatosis, glomeruloid hemangioma or papillary intralymphatic angioendothelioma. Immunohistochemical analyses can generally distinguish these entities easily, based on immunopositivity for mesothelial and epithelial markers (calretinin, WT1, AE1/AE3 and CK5/6). However, the unique features of cellular nodules within lymphovascular channels can occasionally pose significant diagnostic challenges, especially in routine surgical pathology practice.

We would like to know the pathogenesis and pathophysiological mechanism(s) underlying the development of BMNR in the present case, which might represent a possible new entity within acquired cutaneous lymphangiectasia. In line with the three reported cases of cutaneous lymphatic BMNR,[1–3] the significantly accelerated intraabdominal pressure might have had various causes, including a huge ovarian tumor and/or severe ascites, leading to the obstruction of local lymphatic drainage and resulting in the passive mechanical transport of the peritoneal mesothelial/inflammatory nodules. This mechanism is very similar to the mesothelial cell inclusions within lymph nodes, as previously reported.[1,4] It is well known that the intercellular stomas of the parietal peritoneum connect the peritoneal cavity and submesothelial to cutaneous lymphatic vessels.[1] In this scenario, our cutaneous BMNR within acquired lymphangiectasia might have been facilitated by the gradient of abdominal pressure that occurred secondarily to the huge ovarian clear cell carcinoma and ascites. In fact, the submitted omentum also contained numerous inflammatory granulation-like nodules lined by mesothelial cells, corresponding to the histopathology of the BMNR.

In our opinion, BMNR in the cutaneous lymphatics could be more common than generally considered, and we propose that these unique features may constitute a new clinicopathological entity, which should be named ‘benign peritoneal granulation reflux’ rather than ‘BMNR’. Thus, all pathologists should be aware that we can readily misinterpret this form of BMNR as the lymphatic dissemination of carcinoma cells, or frequently miss its tiny foci. Nevertheless, it would be intriguing to assess the significance of the histopathological findings of BMNR and its enigmatic etiology in future larger studies. This short report, taken together with potentially specific findings of a new entity, BMNR in the cutaneous lymphatics, might promote interest within the scientific community.

DISCLOSURE STATEMENT

None declared

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Motona Kumagai,[1] Sohsuke Yamada,[1,2] Nozomu Kurose,[1,2] Satoko Nakada,[1,2] Akane Aikawa,[1,2] Chizuru Futatsuya,[1] Ken-ichi Mizutani,[1] Akihiro Shioya,[1] and Hiroshi Minato[1,3]
[1]*Department of Pathology and Laboratory Medicine, Kanazawa Medical University, Ishikawa*, [2]*Department of Pathology, Kanazawa Medical University Hospital, Ishikawa, and* [3]*Department of Diagnostic Pathology, Ishikawa Prefectural Central Hospital, Ishikawa*

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