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CASE REPORT

A microvenular hemangioma with a rare expression of progesterone receptor immunocreativity and a review of the literature

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Microvenular hemangioma (MVH) is a rare benign vascular tumor with a controversial etiology, but hormone receptor alterations might be involved. We report a case of MVH in a 41-year-old Taiwanese woman who presented with a 1.5 × 1 cm violaceous plaque on left thigh that had appeared 1 year previously. She had taken oral contraceptives for several years and stopped 1 year prior to presentation. Histologically, the tumor was composed of small and compressed venous structures infiltrating in the dermis and subcutis. Immunohistochemically, the tumor cells displayed negative immunoreactivity for human herpesvirus-8 and positive immunoreactivity for smooth muscle actin and progesterone receptor (PR). Taken together with the patient's medical hormone therapy history and the evidence of PR immunoreactivity, our findings support that progesterone may be associated with the tumorigenesis of MVH.

KEYWORDS

immunohistochemistry, microvenular hemangioma, progesterone receptor, vascular tumor

1 | INTRODUCTION

Microvenular hemangioma (MVH) is a rare vascular tumor that can clinically be mistaken for a malignancy. MVH was first described in 1989 by Bant et al.[1] The clinical presentation of MVH is variable, but it is typically an asymptomatic, reddish, firm papule that can develop at any site. The diagnosis of MVH is sometimes challenging. The use of immunohistochemistry now provides us with better approaches for this rare vascular tumor. To the best of our knowledge, only 64 cases have been reported, with 60 cases in the English literature.[1–19] However, the etiology and origin of MVH remain uncertain.[17] We report a rare MVH case in a 41-year-old Taiwanese female, with clinicopathological characteristics and emphasis on its possible tumorigenesis survey. The patient described here is the first MVH case reported in Taiwan.

2 | CASE REPORT

A 41-year-old woman presented with a 1.5 × 1 cm asymptomatic, violaceous and firm plaque on her left posterior thigh. The tumor had been present for 1 year and had seemed to remain the same color and size. She denied any trigger, such as infection, insect bite, trauma history, or change in menstrual periods. Her past medical history included a total thyroidectomy because of non-toxic thyroid goiter 4 years previously, and she had being taking thyroxine since then. She had also been taking oral contraceptives for years, but had stopped 1 year previously. No related family history was noted. A physical examination revealed a non-tender, violaceous, non-blanchable and firm plaque on her left posterior thigh (Figure 1A). The clinical differential diagnoses included dermatofibroma and skin appendage tumors. Excision was performed. After excision, no tumor recurrence has been noted during 6 months of follow-up.

Histologically, the hematoxylin and eosin stained sections showed a poorly circumscribed, infiltrative dermal tumor composed centrally of small vascular structures and concentrically of a proliferation of perivascular spindle cells. The tumor extent included the dermis and subcutis. The vascular lumens were collapsed and branching (Figure 1B, C). Neither mitotic figures nor cellular atypism were conspicuous. The tumor cells revealed monotonous, mildly hyperchromatic nuclei, and small nucleoli. Some intermingling lymphocytic infiltration was noted. Immunohistochemical staining for CD34 and CD31 highlighted the compressed vascular lumens. Staining for smooth muscle actin highlighted concentrated layers of pericytes that surrounded the vascular lumens and revealed focally positive

Yi-Chen Juan and Chih-Jung Chen contributed equally to this study.

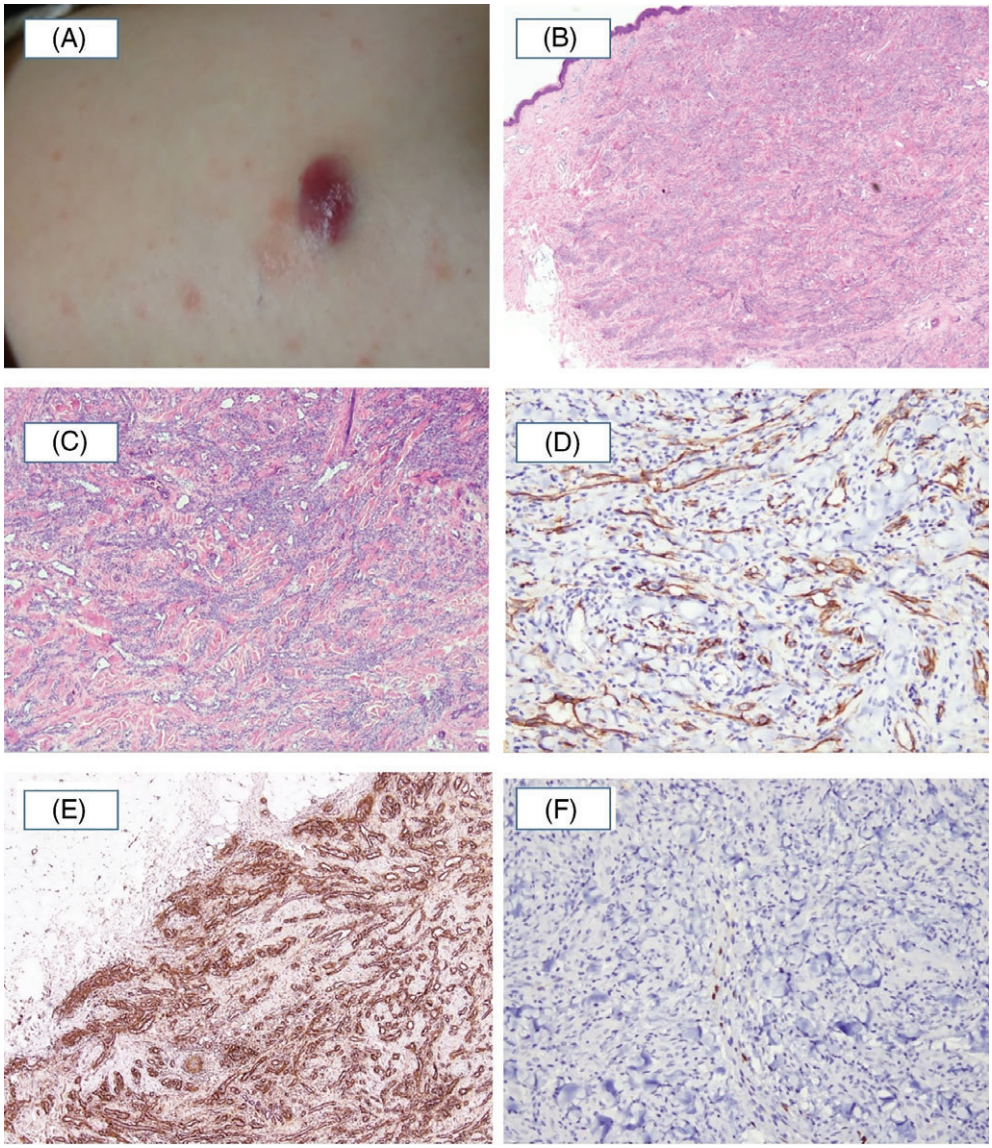

FIGURE 1 (A) A 1.5 × 1 cm asymptomatic violaceous and firm plaque on left posterior thigh. (B) and (C) The specimen showed a poorly circumscribed, infiltrative tumor composed centrally of small vascular structures and a concentric proliferation of perivascular spindle cells (B, hematoxylin and eosin [H&E], × 100; C, H&E, × 200). The tumor involved the dermis and subcutis. Immunohistochemical staining showed CD34(+) in the compressive vascular endothelial cells (D, × 200), smooth muscle actin (+) in the pericyte component (E, × 200) and progesterone receptor (+) (F, × 200)

immunoreactivity for progesterone receptor (PR) (Figure 1D-F). The MIB1 labeling index was very low. Other stains, such as estrogen receptor (ER), androgen receptor (AR), D2-40, Wilms Tumor 1 (WT-1), and desmin, were all negative in our case. In addition, a survey for possible viral infection using the Epstein-Barr virus-encoded small RNA (EBER) in situ hybridization showed a negative result, as did a human herpesvirus-8 (HHV-8) immunohistochemical stain.

3 | DISCUSSION

MVH was first reported in 1989 by Bantel et al,[1] with three cases. All three cases were in females; two of the patients were pregnant and one had recently changed her oral contraceptives. Two years later, Hunt et al reported 10 cases that shared the same histopathologic findings and termed them "MVHs."[2] To the best of our knowledge, at present, 64 cases have been reported.[1–19] Table 1 summarizes the clinical characteristics of MVH.

MVH is a benign hemangioma with a slight female predominance (1.5:1). It often appears in young-to-middle-aged adults (median age: 32.2 years), and the tumors are often solitary, but may present as multiple lesions. MVH is usually a painless, red to brownish, firm, and solitary papule, plaque, or nodule. It usually occurs on the trunk and extremities, but lesions on the head and neck have been occasionally reported. Most patients are healthy individuals, but patients with several comorbidities are also reported, including one case with acute myeloid leukemia,[6] one case with Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes (POEMS) syndrome, and one case with Wiskott-Aldrich syndrome.[5,7] However, the association with malignancy remains unknown.

TABLE 1 Clinicopathological Features of Microvenular Hemangioma[1–19]

Age	Median: 32.2 years; range: 16 months to 69 years
Sex	33 females and 22 males
Comorbidity	Acute myelogenous leukemia (BMT), asthma, hypertension, hypothyroidism, total thyroidectomy, POEMS syndrome, Wiskot-Aldrich syndrome, and lymphoma
Trigger	Oral contraceptive; pregnancy
Site	Trunk: 29 Extremities: 28 Head and neck: 2
Solitary or multiple	Solitary: 53 Multiple: 11
Immunohistochemical stain	CD31: Positive in 21/21 CD34: Positive in 30/30 SMA: Positive in 25/25 HHV-8: Negative in 14/15 D2–40: Negative in 26/27 WT-1: Positive in 20/21 Factor VIII related antigen: Positive in 22/22 GLUT-1: Negative in 10/11 HHF-35: Positive in 3/3 UEA-1: Positive in 11/11 ERG: Positive in 2/2 PR: 1/1

Abbreviations: SMA, smooth muscle actin; HHV-8, human herpes virus 8; WT-1: Wilms Tumor 1; GLUT-1, glucose transporter 1; UEA-1, Ulex europaeus I; ERG, Ets-related gene; PR, progesterone receptor

MVH is characterized by a proliferation of poorly circumscribed, haphazardly infiltrated, small, thin-walled, venous vessels involving the reticular dermis. The vascular lumens are usually collapsed and have a slit-like appearance. The vessels are surrounded by a layer of pericytes. The pericytes are plump spindle cells with ovoid nuclei and a moderate amount of blue-gray cytoplasm. Inflammation is usually minimal, with little lymphocyte infiltration. Atypical cells are absent in MVH.

The diagnosis of MVH is challenging and has to be differentiated from malignant lesions, such as patch-stage Kaposi sarcoma (KS) and angiosarcoma, as well as from other entities of hemangioma, including targetoid hemosiderotic hemangioma, acquired tufted angioma, and lobular capillary hemangioma. Patch-stage KS presents with anastomosing vascular spaces, rather than collapsed vascular lumens. Some features of KS, such as hyaline globules, plasma cells, fascicles of spindle cells, or the promontory sign, are lacking in MVH. Moreover, HHV-8 is absent in MVH. Angiosarcoma can be distinguished from MVH by the presence of cytologic atypia and the absence of a pericyte layer.

Targetoid hemosiderotic hemangioma shares similar clinical features with MVH. Targetoid hemosiderotic hemangioma consists of dilated vascular lumens that are lined by hobnail cells, and it shows WT-1 and D2-40 positivity. By contrast, MVH is negative for D2-40.[11] Acquired tufted angioma has a distinctive "cannonball" distribution, which is not seen in MVH. The positive finding of D2-40 can also distinguish tufted angioma from MVH.

Although the differential diagnosis of MVH may be difficult, several immunochemical stains may help us to approach this rare vascular tumor. We have summarized the immunochemical stain results of previous case reports in Table 1. Generally, most cases show increased numbers of CD34-positive fibrocytes in the dermis surrounding the hemangioma. This finding may hint that MVH is a reactive vascular proliferation. However, CD34(+) is not specific for reactive processes, and the nature and history of previous cases do not support this hypothesis. D2-40 and glucose transporter 1 stainings are negative in most MVH cases. Cytoplasmic immunoreactivity for WT-1 protein was observed, and this supports the classification of MVH as a vascular neoplasm.

Currently, MVH is classified as a vascular origin neoplasm with proliferating cells of an endothelial nature and pericytes around the proliferating capillaries and venules. The pathogenesis of MVH is still unknown. After reviewing the previous case reports and comparing their features to our own case, we hypothesized that some associations might exist between hormones and MVH. However, no previous studies have provided evidence for this hypothesis, and no hormone receptor studies have been performed. To confirm our hypothesis, we performed immunochemical staining for the PR, ER, and AR on our specimen, and we found focally positive staining for the PR only. This positive finding would appear to support our assumption that progesterone may be associated with the tumorigenesis of MVH, but further study will be needed to confirm our results.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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