An unusual presentation of glomeruloid hemangioma in a patient with VHL syndrome: A case report and review of literature

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ABSTRACT

Von Hippel-Lindau (VHL) is an inherited neoplasia syndrome caused by inactivation of the VHL tumor suppressor gene, characterized by the development of sporadic clear cell renal carcinoma, pheochromocytomas, retinal angioma, pancreatic cysts, and CNS hemangioblastomas. Glomeruloid hemangioma is a vascular lesion, previously considered to be specifically associated with POEMS (polyneuropathy, organomegaly, endocrinopathy/edema, M-protein and skin abnormalities) syndrome. However, there are reports of solitary glomeruloid hemangioma in patients without POEMS syndrome. We report the case of a 39-year-old male with VHL disease, with known bilateral clear cell renal carcinomas, CNS hemangioblastoma and pancreatic cysts. The patient presented with a 0.35 cm red papule on the left lateral neck, which was easily irritated, and bleed frequently. Histopathologically, there were irregular areas of ectatic vascular channels of small capillaries, resembling renal glomeruli, surrounded by actin-positive pericytes, within the dermis. These findings were consistent with a glomeruloid hemangioma. Fluorescent in-situ hybridization studies confirmed a deletion in the 3p25.3 region. As per clinical tests, no evidence of POEMS syndrome was found in this patient. Only six reports of glomeruloid hemangioma have been previously reported in patients without POEMS syndrome and this constitutes the first report of glomeruloid hemangioma in a patient with VHL.

Keywords: Von Hippel-Lindau (VHL); Glomeruloid Hemangioma; POEMS; Immunohistochemical Stain; Fluorescent in Situ Hybridization (FISH) Analysis

1. INTRODUCTION

Von Hippel-Lindau (VHL) disease is a rare autosomal dominant hereditary disorder with variable expression and multi-organ manifestations including hemangioblastoma of the retina and central nervous system, pancreatic cysts, pheochromocytoma/paraganglioma, renal cysts and renal cell carcinoma (RCC) [1]. The responsible gene of VHL disease was identified in 1993 on the short arm of chromosome 3 [2-4].

POEMS (polyneuropathy, organomegaly, endocrinopathy/edema, M-protein and skin abnormalities) syndrome, which was first reported in 1968, is a multisystem disease [5]. Glomeruloid hemangiomas are benign vascular tumors comprised by dilated vascular spaces filled by aggregates of small capillary vessels, morphologically resembling renal glomeruli. This lesion was first introduced as a distinctive vascular proliferation occurring in patients with POEMS syndrome [6].

2. CASE REPORT

Our patient, who was diagnosed with VHL in 2002, underwent multiple surgeries for clear cell renal cell carcinoma, cerebellar and spinal hemangioblastomas, as well as pancreatic cysts. He was treated with Vandetanib since November 2010 and developed a phototoxic reaction to this drug. His family history is significant for VHL syndrome in his mother and grandfather. Both of them passed away due to renal cell carcinoma with kidney failure. He presented to the Dermatology Clinic at the
National Institutes of Health for a follow-up evaluation of the phototoxic reaction, with generalized hyperpigmentation (related to treatment with ZD6474/vandetanib), which developed two months prior. At this time he complained of a skin lesion on the neck for two weeks, which was easily irritated and bled frequently. On physical examination, the lesion was a 0.35 cm pink, scaly papule on the left lateral neck (Figure 1(A)). Clinically, the lesion had features suspicious for angioma or skin cancer. No other cutaneous lesions were evident.

A biopsy taken from the papule showed hyperkeratosis with focal destruction of basal epidermal layers and a band-like lymphohistiocytic infiltrate in the upper dermis. The reticular dermis revealed closely arranged, dilated irregular-shaped vascular spaces, containing capillaries with nodular manner resembling renal glomeruli (Figures 1(B) and (C)). Histologic features diagnostic of malignancy, such as increased mitosis and necrosis, were not observed. The histophenotypic findings were consistent with a glomeruloid hemangioma. No evidence of POEMS was found on physical examination or multiple laboratory and imaging studies.

VHL disease is caused by mutations in the VHL gene on chromosome 3p25.3. Fluorescent in-situ hybridization studies using the CEP3 centromere probe for chromosome 3 and the VHL probe, showed deletion of the region containing the VHL gene (Figure 2), confirming the diagnosis of VHL in this patient.

2.1. FISH Analysis of the VHL Gene Deletion on Paraffin-Embedded Hemangioma Tissue Sections

For tumor interphase FISH analysis, BAC clone RP11-438J1 (210kB) including the entire VHL gene from the 3p25.3 region was used. The VHL BAC DNA probe labeled by SpectrumOrange was purchased from Empire Genomics (Buffalo, NY). Centromere enumeration probe for chromosome 3 (CEP3) labeled with SpectrumGreen was purchased from (Abbott Molecular, Chicago, IL). FISH assays were performed on 5-micron Formalin Fixed Paraffin Embedded (FFPE) tumor sections using laboratory standardized protocol with slight modification [7]. A total of minimum 100 nuclei were scored for each specimen.

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3. DISCUSSION

There are numerous nonspecific cutaneous manifestations in POEMS syndrome [8]. Multiple angiomas can occur in 26% of the patients with POEMS syndrome [9,10]. VHL results from a mutation in the Von Hippel-Lindau tumor suppressor gene on chromosome 3p25.3. In VHL, the main manifestations are angiomatosis, hemangioblastoma, pheochromocytoma, renal cysts, renal cell carcinoma, pancreatic cysts (pancreatic serous cystadenoma) and café au lait spots [11]. Our patient developed diffuse hyperpigmentation due to photosensitivity associated with Vandetanib (ZD6474) therapy, an inhibitor of epidermal growth factor receptor, vascular endothelial growth factor receptor, and the RET (rearranged during transfection) kinases. Hyperpigmentation due to photosensitivity with Vandetanib therapy has been previously reported by Kong and coworkers [12].

To the best of our knowledge, there is no report of glomeruloid hemangiomas in VHL patients. Less than 25 cases of glomeruloid hemangioma in POEMS syndrome have been reported and this lesion was considered to be a dermatopathologic marker of POEMS syndrome. However, in the literature, there are six reports of glomeruloid hemangioma in patients without POEMS (summarized in Table 1) [13-18]. The average age for this group of patients is 57 years old (range: 29 - 86) with a male to female ratio is 7:3.

![Figure 1](image1.png)

**Figure 1.** Clinical image of the scaly, pink papule on left lateral neck (A); H&E stained section at 200× magnification (B); H&E stained section at 400× magnification (C).

![Figure 2](image2.png)

**Figure 2.** Dual-color FISH showing loss of the VHL gene copy (Red fluorescence signal) in the tumor cells compared to the control Chromosome 3 centromeric probe (Green fluorescence signals). Ratio of red:green <0.8.
Table 1. Summary of reported cases with glomeruloid hemangioma in the patients without POEMS syndrome.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Number of lesion</th>
<th>Anatomic location</th>
<th>Underlying diseases</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>F</td>
<td>Solitary</td>
<td>Uterus</td>
<td>Breast and endometrial carcinomas</td>
<td>Giner et al. [13]</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>M</td>
<td>Solitary</td>
<td>Scalp</td>
<td>Hypertension, and bilateral carpal tunnel syndrome</td>
<td>González-Guerra et al. [14]</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>M</td>
<td>Solitary</td>
<td>Lateral neck</td>
<td>Hypertension and DM type 2</td>
<td>Lee et al. [15]</td>
</tr>
<tr>
<td>4</td>
<td>78</td>
<td>F</td>
<td>Solitary</td>
<td>Cheek</td>
<td>Hypertension and DM type 2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>F</td>
<td>Solitary</td>
<td>Unknown</td>
<td>None</td>
<td>Forman et al. [16]</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>M</td>
<td>Solitary</td>
<td>Unknown</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>53</td>
<td>M</td>
<td>Solitary</td>
<td>Unknown</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>46</td>
<td>M</td>
<td>Multiple</td>
<td>Trunk</td>
<td>None</td>
<td>Piña-Oviedo et al. [17]</td>
</tr>
<tr>
<td>9</td>
<td>86</td>
<td>M</td>
<td>Solitary</td>
<td>Face</td>
<td>Hypertension, DM type 2 and chronic bronchitis</td>
<td>Vélez et al. [18]</td>
</tr>
<tr>
<td>10</td>
<td>39</td>
<td>M</td>
<td>Solitary</td>
<td>Lateral neck</td>
<td>VHL</td>
<td>Current case</td>
</tr>
</tbody>
</table>


The histogenesis of glomeruloid hemangiomas remains unclear. Studies have postulated that it is probably due to reactive endothelial proliferation and the overproduction of vascular endothelial growth factor 6 [19]. Eosinophilic globules, within the cytoplasm of some endothelial and stromal cells have been reported in glomeruloid hemangiomas. It has been postulated that the PAS-positive cytoplasmic material of endothelial and plump cells might represent immunoglobulins. In our case, a polytypic pattern of light chain immunoglobulins (kappa and lambda) is seen in PAS-positive hyaline globules containing cells (data not shown), as previously reported by Chan et al. All endothelial cells in our case are positive for CD31 and CD34 (data not shown).

Suurmeijer described that immunostaining of basement membrane for collagen type IV highlighted discriminating features between papillary hemangiomas (thin) and glomeruloid hemangiomas (thick) [20]. The immunostain of collagen type IV in our case showed thick basement membrane-like matrix enveloping pericytes (data not shown) as previously described in glomeruloid hemangiomas.

In our case, the lesion is single and developed in a patient with VHL disease. Although angiomatosis in several organs is one of the features of VHL syndrome, there has been no report of glomeruloid hemangioma in patients with VHL. This report further suggests that glomeruloid hemangioma is not necessarily a marker of POEMS and can also be seen in the patients with VHL syndrome.

REFERENCES


