Case Report
Parotid Oncocytoma as a Manifestation of Birt-Hogg-Dubé Syndrome

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Received 8 January 2018; Accepted 7 May 2018; Published 3 June 2018

Academic Editor: Bruce J. Barron

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Birt-Hogg-Dubé syndrome (BHD) is a rare autosomal dominant disease characterized by skin fibrofolliculomas, pulmonary cysts, spontaneous pneumothoraces, and renal cancers. Oncocytomas are benign epithelial tumors that are also rare. Recently, there have been a few case reports of BHD with a parotid oncocytoma that appear to have a BHD phenotype. Here we document the eighth known case and describe the magnetic resonance imaging features of the parotid oncocytoma, which mimicked Warthin’s tumor. Radiologists should be aware of the association between these rare disorders.

1. Introduction

Birt-Hogg-Dubé syndrome (BHD) is a rare autosomal dominant disease characterized by skin fibrofolliculomas, pulmonary cysts, spontaneous pneumothoraces, and renal cancers [1]. In 1977, Birt, Hogg, and Dubé reported on a group of patients from single kindred who had multiple fibrofolliculomas with trichodiscomas and acrochordons [2]. This hereditary condition was later named Birt-Hogg-Dubé syndrome. In 2002, Nickerson et al. identified the BHD gene, which codes a protein called folliculin [3]. The BHD gene is now known as the folliculin gene (FLCN).

Patients with BHD often have renal tumors. Pavlovich et al. reported that 34 (27%) of 124 patients with BHD had renal tumors with variable histology, most commonly hybrid oncocyic tumors, and chromophobe renal cell carcinomas [4]. However, there are few reported cases of BHD with parotid gland oncocytoma. Here we present a rare case of a patient with this association.

2. Case History

A 44-year-old woman presented to our hospital complaining of right lower facial swelling and pain around the parotid gland. Her past medical history was unremarkable. However, she had a family history of pneumothoraces in her father and brother. Magnetic resonance (MR) imaging showed a 35 mm diameter mass in the superficial lobule of the right parotid gland. The lesion appeared hypointense on both T1-weighted MR imaging (T1WI) and T2-weighted imaging (T2WI). On fat-saturated T2WI, the masses appeared hyperintense when compared with the native parotid gland tissue but hypointense on contrast-enhanced T1WI with fat saturation. The lesion was hyperintense on axial diffusion-weighted imaging with a b-value of 1000 s/mm² and a low apparent diffusion coefficient (Figure 1). The lesion was suspected to be Warthin’s tumor, and a right superficial parotidectomy was performed accordingly.
There was a well-circumscribed, solid, mahogany-colored nodule measuring 3.7 × 2.8 × 2.4 cm in the superficial parotidectomy specimen (Figure 2(a)). Microscopically, the nodule was an encapsulated tumor containing oncocytic cells. These cells formed solid clusters or trabecular patterns, separated by thin strands of fibrovascular stroma (Figure 2(b)) and were round in shape with centrally placed nuclei and clear cytoplasm. Neither necrosis nor capsular invasion was observed. Cytoplasmic granules enriched with glycogen were present but there was no mucin on periodic acid-Schiff staining (data not shown). Although the morphology was comparable to oncocytoma of the kidney, radiologic examination excluded the possibility of a metastatic renal tumor, and immunostaining for PAX-2 and CD10, which are markers for renal cell carcinoma, was negative (data not shown). The pathologic diagnosis was clear cell oncocytoma.

One and a half years later, the patient presented to hospital again, this time with mild dyspnea. Physical examination revealed decreased breath sounds on the right side. A computed tomography (CT) scan showed a right pneumothorax and multiple cysts. The cysts were located in the medial basilar regions of the lung fields bilaterally and were ellipsoid in shape and variable in size. Some of the cysts abutted the proximal portions of the lower pulmonary arteries (Figure 3). The patient was strongly suspected to have BHD and was subsequently referred for genetic counseling. Informed consent was obtained from the patient for FLCN genetic testing, which was performed on genomic DNA extracted from
Figure 2: Histopathologic findings of parotid clear cell oncocytoma. (a) A well-circumscribed, solid, mahogany-colored nodule. (b, c) Microscopically, fibrous encapsulated nodules containing oncocytic tumor cells with a clear cytoplasm. (hematoxylin-eosin staining; original magnification, 20× in (b) and 400× in (c))

Figure 3: Pulmonary computed tomography demonstrating a right pneumothorax and multiple cysts (arrow). An ellipsoidal cyst abuts on the proximal portion of the pulmonary artery.

Peripheral leukocytes. Duplication of cytosine was identified in the C8 tract of exon 11 (c.1285dupC), confirming the diagnosis of BHD. The patient’s brother, who had an episode of pneumothorax, asked for genetic testing and was found to have the same mutation as the proband (data not shown).

3. Discussion

BHD is a rare disease and there are some reports of its prevalence. In North America, 102 BHD-affected families have been reported by the National Cancer Institute group.
and usually occur in the seventh to ninth decades of life. Tumors are slightly more prevalent in women than in men for 78%–84% of salivary gland oncocytomas [12]. These parotid gland is the site most often affected, accounting for only 0.5%–1.5% of all salivary gland tumors. The oncocytomas are rare benign epithelial tumors, accounting for 0.5%–1.5% of all salivary gland tumors. The cysts, renal tumors, and cutaneous manifestations is limited. Regarding the manifestations of BHD apart from pulmonary cysts, renal dominance were characteristic features of BHD on CT [20]. Cysts abutting or including the proximal portion of the lower pulmonary arteries or veins are also highly probable in BHD (Figure 3). Our patient had these features, which were very helpful in making a diagnosis of BHD.

In conclusion, we describe the eighth confirmed case in the literature of parotid oncocytoma in BHD, which mimicked Warthin’s tumor on MR imaging. Parotid oncocytoma appears to be one of the phenotypes in BHD. It is difficult to distinguish between oncocytomas and Warthin’s tumors; however, radiologists should be aware of this association and consider parotid oncocytoma as a differential diagnosis if they detect a parotid mass similar to Warthin’s tumor in BHD. If additional imaging is to be recommended, a dedicated renal-protocol MRI would be the choice, alone or in addition to chest CT.

Consent

Informed consent to publish this report was obtained from the patient.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.
<table>
<thead>
<tr>
<th>Case</th>
<th>Year</th>
<th>First author and region</th>
<th>Age at diagnosis</th>
<th>Sex</th>
<th>Mutation</th>
<th>Pathology of parotid tumor</th>
<th>Skin</th>
<th>Lung</th>
<th>Kidney</th>
<th>Family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2000</td>
<td>Liu et al. [5]</td>
<td>56 M</td>
<td>M</td>
<td>N/A</td>
<td>Oncocytoma (55)</td>
<td>FF</td>
<td>PTX</td>
<td>N/A</td>
<td>N/A Sister (PTX, LC)</td>
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<td>2-4</td>
<td>2000</td>
<td>Schmidt et al. [6]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Oncocytoma N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>5</td>
<td>2011</td>
<td>Maffé et al. [7]</td>
<td>53 F</td>
<td>M</td>
<td>c.347dupA (exon 5)</td>
<td>Oncocytoma (32, right; 43, left)</td>
<td>FF</td>
<td>PTX</td>
<td>LC</td>
<td>Father (PTX)</td>
</tr>
<tr>
<td>6</td>
<td>2012</td>
<td>Lindor et al. [8]</td>
<td>45 F</td>
<td>F</td>
<td>c.779+1G&gt;T (exon 7)</td>
<td>Oncocytic neoplasm (45)</td>
<td>FF</td>
<td>PTX</td>
<td>LC</td>
<td>Maternal grandfather (prostate cancer), maternal grandmother (bladder cancer, lung cancer)</td>
</tr>
<tr>
<td>7</td>
<td>2013</td>
<td>Pradella et al. [9]</td>
<td>N/A</td>
<td>N/A</td>
<td>c.347dupA (exon 5)</td>
<td>Oncocytoma (45)</td>
<td>FF</td>
<td>PTX</td>
<td>LC</td>
<td>Father (PTX)</td>
</tr>
<tr>
<td>8</td>
<td>2016</td>
<td>Present report</td>
<td>45 F</td>
<td>F</td>
<td>c.1285dupC (exon 11)</td>
<td>Clear cell oncocytoma (44)</td>
<td>FF</td>
<td>PTX</td>
<td>LC</td>
<td>Brother (PTX)</td>
</tr>
</tbody>
</table>

M: male; F: female; FF: fibrofolliculoma; TD: trichodiscomas; PTX: pneumothorax; LC: lung cysts; CCC: clear cell carcinoma; N/A: not available.
Table 2: Imaging features of parotid oncocytoma.

<table>
<thead>
<tr>
<th>No.</th>
<th>First author, year</th>
<th>Age/Sex</th>
<th>BHD or not</th>
<th>Pathology</th>
<th>Size (mm)</th>
<th>CT enhancement</th>
<th>MRI T1WI</th>
<th>MRI T2WI</th>
<th>MRI DWI/ADC</th>
<th>MRI T2WI FS</th>
<th>MRI TIW1CE FS</th>
<th>FDG-PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kasai et al. [10] 2007</td>
<td>56/F</td>
<td>Onc</td>
<td>25</td>
<td>N/A</td>
<td>Hypo</td>
<td>Hypo</td>
<td>High/Low</td>
<td>Iso</td>
<td>Iso</td>
<td>N/A</td>
<td></td>
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<tr>
<td>2</td>
<td>Shah et al. [11] 2007</td>
<td>76/M</td>
<td>Onc</td>
<td>20</td>
<td>Homogeneous</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Intense FDG uptake</td>
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<tr>
<td>3-12</td>
<td>Tan et al. [12] 2010</td>
<td>49–74/7 female/3 male</td>
<td>Onc</td>
<td>6–66</td>
<td>Homogeneous</td>
<td>6</td>
<td>Hypo 4</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>13-21</td>
<td>Patel et al. [13] 2011 N/A</td>
<td>6 female/3 male</td>
<td>Onc 1*</td>
<td>13–34</td>
<td>Hypo</td>
<td>N/A</td>
<td>8 Iso 1 Hyper*</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>22</td>
<td>Lindor et al. [8] 2012</td>
<td>45/F BHD</td>
<td>Onc</td>
<td>9</td>
<td>N/A</td>
<td>Hypo</td>
<td>Hyper</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>23</td>
<td>Sepulveda et al. [14] 2014</td>
<td>67/F BHD</td>
<td>Onc</td>
<td>73</td>
<td>Heterogeneous</td>
<td>N/A</td>
<td>N/A</td>
<td>Hyper</td>
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<td>N/A</td>
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<td>24</td>
<td>This report Yoshida et al.</td>
<td>44/F BHD</td>
<td>Clear cell Onc</td>
<td>35</td>
<td>N/A</td>
<td>Hypo</td>
<td>Hypo</td>
<td>High/Low</td>
<td>Hyper</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

M: male; F: female; Hypo: hypointense; Iso: isointense; Hyper: hyperintense; N/A: not available; T1WI: T1-weighted imaging; T2WI: T2-weighted imaging; DWI: diffusion-weighted images; ADC: apparent diffusion coefficient; T2WI FS: T2-weighted imaging with fat saturation; TIW1CE FS: post contrast T1-weighted imaging with fat saturation; FDG-PET: 18F-fluorodeoxyglucose positron emission tomography; Onc: oncocytoma.

* Mixed oncocytoma/pleomorphic adenoma.
Acknowledgments

The authors thank Dr. Shojiro Morinaga, Department of Pathology, Hino Municipal Hospital, Hino, Japan, for making the pathological diagnosis in this patient.

References
