Second Branchial Cleft Cyst

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History

A 31 year old white female presented with complaints of an enlarging right sided neck mass of 1.5 months. She reported fluctuation in size over the past month. Her primary care physician prescribed antibiotics but the mass did not decrease in size. On physical examination, the patient was afebrile. A 2 cm mobile non tender mass was palpated in the right neck. The rest of the head and neck physical examination was unremarkable. A fine needle aspiration was performed that showed abundant squamous cells present, some with mild atypia in a background of debris devoid of lymphocytes. Purulent liquid was aspirated which decreased the neck mass.

Radiographic Features

Axial computed tomography (CT) imaging demonstrated a rounded low density $2.9 \times 2.8 \times 3.6$ cm cystic mass with a non-enhancing wall at the junction of levels 2A and 3 in

the right neck (Fig. 1a). The mass was posterior to the submandibular gland, anterior to the carotid space, and anteriomedial to the sternocleidomastoid muscle. Ultrasonographic examination revealed a hypoechoic mass with no solid component or internal vascularity (Fig. 1b).

Diagnosis

On gross examination of the surgically excised mass a soft, compressible, fluctuant 5.0×3.5 cm encapsulated lesion was identified. On bisecting the mass a unilocular cyst containing brown mucoid material was seen (Fig. 2). The cyst lining was smooth with no papillary projections or areas of hemorrhage.

The hematoxylin and eosin (H&E) showed a cyst lined by stratified squamous epithelium with keratinaceous debris present in the cyst lumen (Fig. 3). The stroma adjacent to the epithelium contained areas of lymphoid tissue with reactive germinal centers but lacked true lymph node architecture. On higher power no epithelial dysplasia or nuclear pleomorphism was seen and a well-developed basement membrane was present (Fig. 4a). The cyst lining showed moderately strong nuclear and cytoplasmic immunoreactivity for p16 by immunohistochemistry, however the expression was confined predominantly to the basal and parabasal cells (Fig. 4b). Based on the clinical, radiographic and microscopic findings the final diagnosis was second branchial cleft cyst.

Discussion

Second branchial cleft cysts are benign developmental cysts thought to arise from congenital remnants of the

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Fig. 1 **a** An axial CT image with contrast shows a well-circumscribed cystic mass in the right neck, posterior to the submandibular gland and anterior to the sternocleidomastoid muscle. There is no significant solid or nodular component or surrounding infiltration of

the fat. **b** Sonographic examination revealed a hypoechoic mass with no solid component or internal vascularity. The wall appeared thin and nearly imperceptible. The mass is anterior and slightly medial to the carotid artery and jugular vein (shown on *color Doppler*)

Fig. 2 **a** Gross examination of the bisected cyst reveals a smooth surface lining of uniform thickness without papillary projections. **b** Thick mucoid material found within the cyst. This mucoid material can alter the radiographic imaging of a branchial cleft cyst

second branchial arch. Other branchial anomalies exist but are much less common than second cleft anomalies which represent >95 % of all branchial cleft anomalies [1, 2]. Second branchial cleft cysts are usually located in the lateral neck anterior to the sternocleidomastoid muscle. The majority of cases arise in young patients between the age of 20 to 40 years of age although branchial cleft cysts can present in infants and children <5 years old. Fistulae or sinuses are more common in infants or young children and present as chronic drainage from an opening in the lateral neck. Rarely, second branchial cleft cysts arising in older

patients have been reported. There is no gender predilection.

Clinically the presentation is of a painless compressible swelling situated at the anterior border of the sternocleidomastoid muscle between the mandibular angle and clavicle. The patient may report that the swelling is of long duration with periods of waxing and waning. Acute size increase can occur during upper respiratory tract infection. Secondary infections and inflammation can occur. Although unusual, bilateral second branchial cleft cysts have been reported and in some patients this is part of the

branchio-oto-renal syndrome, an autosomal dominant disorder [1]. Mapped to chromosome 8q 13.3, other symptoms include hearing impairment, cup-shaped pinnae, preauricular pits, branchial fistulae and renal anomalies.

The treatment for second branchial cleft cysts is surgical resection approached by a transverse cervical incision [1]. The cysts can be located either superficial or deep to the

Fig. 3 Low power image of a second branchial cleft cyst lined by stratified squamous epithelium. Keratinaceous debris is noted in the lumen. Lymphoid aggregates with germinal centers are identified subjacent to the epithelium

cervical fascia. Careful dissection around the cyst bed and exploration for an associated fistula is required. If there has been a history of infection and/or inflammation, subsequent scarring can make complete surgical excision challenging.

The differential diagnosis includes other lateral neck swellings [1]. The most important differential diagnosis is metastatic cystic squamous cell carcinoma to a lymph node from an oropharyngeal HPV-associated squamous cell carcinoma. Any new lateral neck mass in an adult >30 years of age must be considered malignant until proven otherwise [3, 4]. On radiologic imaging second branchial cleft cysts typically present as round or ovoid masses with a thin enhancing capsule and homogeneous fluid content. This is in contrast to a metastatic cystic lymph node, which most commonly exhibits a thick, irregularly enhancing solid wall with a complex appearance of the central necrotic non-enhancing area. (Figure 5a) however, occasionally a metastatic squamous cell carcinoma may be almost entirely cystic and, hence, can show significant overlap in radiographic appearance with a branchial cleft cyst. Given this fact, metastases should be the first consideration in any adult with a cystic neck mass in this location.

In a published series on the imaging findings of second branchial cleft cysts, approximately 3 % of patients proved to have cystic squamous cell metastases on pathologic examination despite typical CT findings for a second branchial cleft cyst including a solitary cystic lesion with a thin rim and only minimal enhancement [5]. Conversely, secondarily infected second branchial cleft cysts can mimic cystic metastatic lesions [4, 6].

Fig. 4 **a** A thin basement membrane separates the epithelial cells of the branchial cleft cyst from the lymphoid tissue. The squamous epithelium is mature without atypia. **b** p16 immunohistochemistry shows weak immunoreactivity confined primarily to the basal and

parabasal cells of the branchial cleft cyst. This expression pattern is distinctly different from a HPV-associated oropharyngeal carcinoma metastasis

Fig. 5 **a** An axial contrast enhanced CT shows a primary left palatine tonsil mass with an ipsilateral predominantly cystic/necrotic left level II lymph node and a contralateral, more solidly enhancing heterogenous right level II lymph node metastasis. **b** The corresponding fused

PET-CT shows FDG uptake in the primary left palatine tonsil mass and contralateral node, but no FDG uptake in the predominantly cystic node. This is a well-recognized PET pitfall

Ultrasonographic examination of second branchial cysts usually depicts a well-circumscribed cyst. However, there is variability in the ultrasonographic appearance of second branchial cleft cysts when secondary infection is present or when septae or cellular debris is present within the cyst resulting in a pseudosolid or heterogenous appearance [6]. The differential diagnosis can include malignant lymphadenopathy, carotid body tumor, nerve sheath tumor, and inflammatory lesions such as abscess.

Fine needle aspiration (FNA) of cystic neck masses can be challenging. Often the cytologic specimen shows a paucity of epithelial cells and/or degraded epithelial cells or contains inflammatory cells. If the pathologists and treating clinician are concerned for a cystic metastases p16 staining can be done to confirm their suspicion. However p16 staining may be weak or absent and p16 positivity is not unique to HPV positive tumors and has been reported in about half of second branchial cleft cysts [7, 8]. Therefore using p16 to confirm or discount a cystic metastases in FNA specimens can lead to erroneous diagnoses. Although the epithelial lining in branchial cleft cysts shows p16 immunoexpression, the expression pattern differs from metastatic HPV positive oropharyngeal squamous cell carcinoma which shows diffuse and strong nuclear and cytoplasmic staining. This is in contrast to branchial cleft cysts that can show focal nuclear and cytoplasmic staining. Pai et al. [8] demonstrated p16 positivity in 6 of 21 branchial cleft cysts with p16 expression involving the superficial squamous cells lining the cyst without full-thickness staining. No case showed diffuse and strong staining typically seen in HPV positive tumors. Unlike these cases reported by Pai et al., in the current case the p16 expression showed variable patchy staining

involving <50 % of epithelial cells in a similar pattern described by Cao et al. [9] involving the basal and para-basal cells.

The existence of branchial cleft cyst (branchiogenic) carcinoma has been hotly debated [10, 11]. Most authorities believe that cystic squamous cell carcinomas located at the cervical levels II or III are metastatic tumors even when a primary tumor is not detectable. Earlier case reports are generally incomplete, lacking panendoscopy evaluation or imaging studies that evaluate the oropharyngeal area. At this time a diagnosis of branchiogenic carcinoma should be a diagnosis of exclusion. With improved imaging studies, including positron emission tomography (PET) as well as the use of p16 immunohistochemistry and/or high-risk HPV in situ hybridization a primary tumor is usually identified (Fig. 5b). If a primary tumor is not detected despite panendoscopy and tonsillectomy the patient should be followed for a minimum of 5 years before ruling out an occult primary tumor.

Although rare, papillary thyroid carcinoma metastasis presenting as a solitary cervical cyst has been reported. In one series of 37 patients with a solitary cervical cyst, 4 patients (10.8 %) with a mean age of 29 years had papillary thyroid carcinoma [12]. FNA was confirmatory in 1 case while the other 3 cases had histologic confirmation on the resected specimen. Histologic examination should readily differentiate papillary thyroid carcinoma from second branchial cleft cyst. Nasopharyngeal carcinoma presenting clinically as a cystic lateral neck swelling as the initial presentation has been reported and could be misinterpreted as a second branchial cleft cyst. In one study of 136 cases, 8 % of cystic metastases in the lateral neck were of nasopharyngeal origin [13]. Using in situ hybridization

for EBV encoded RNA (EBER) can help to distinguish EBV associated nasopharyngeal carcinoma from HPV associated oropharyngeal carcinoma, although HPV positive carcinomas arising in the nasopharynx occur.

Other lateral neck swellings include bronchogenic cyst and cervical thymic cyst [5]. These cysts are more commonly seen in children than in adults. Although the bronchogenic cyst more commonly occurs in the midline near the sternum it can present in the lateral neck. The bronchogenic cyst is lined by respiratory-type epithelium and the cyst wall is composed of mucoserous glands, hyaline cartilage and smooth muscle; distinctly different from second branchial cleft cysts. The cervical thymic cyst most commonly presents in the anterior cervical triangle but can present anywhere between the angle of the mandible and the sternum. Interestingly thymic cysts are more common on the left than the right side. The cervical thymic cyst is lined by cuboidal, columnar and/or squamous epithelium. The cyst wall contains thymic tissue including Hassall corpuscles and lymphoid follicles.

Midline neck swellings including dermoid cyst, thyroglossal duct cyst and laryngocele have different clinical and radiographic presentations from second branchial cleft cyst. In addition the microscopic features including absence of lymphoid stroma are distinct from second branchial cleft cyst.

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