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Review Article

Squamous carcinoma arising in a branchial cleft cyst: have you ever treated one? Will you?

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Abstract

The existence of primary branchiogenic carcinoma – that is, carcinoma arising in a pre-existing branchial cleft cyst (a benign developmental cyst) – has in recent decades been the subject of increasing scepticism. Recognition of the propensity of a variety of head and neck sites – including in particular the tonsil – to give rise to cervical metastases while the primary tumours themselves remain undetected has given rise to the idea that virtually all cystic carcinomas of the neck represent metastatic deposits, whether or not their primary sites are found. A diagnosis of primary branchiogenic carcinoma should be viewed with extreme scepticism, and every effort should be made (e.g. imaging, panendoscopy, elective tonsillectomy) to exclude the existence of a primary site elsewhere, before considering a diagnosis of primary branchiogenic carcinoma.

Key words: Branchiogenic Carcinoma; Branchial Cleft Cyst; Squamous Cell Carcinoma

Introduction

During the course of human fetal development, arches of tissue in the neck develop which are analoguous to the membranes (gills) of fish. In fish, these aid the extraction of oxygen from water. In humans, these arches (branchial clefts, from the Latin *branchiae*, meaning gills) and their intervening clefts develop not into gills but into a variety of head and neck structures, including contributions to the neck, the jaw, and the middle and external ear.[1] In humans, a host of different developmental anomalies may be associated with these branchial clefts, including cysts, sinuses and fistulae. Chief among these are branchial cleft cysts.[2,3] On physical examination, branchial cleft cysts usually manifest as rounded, non-tender masses situated along the anterior border of the sternocleidomastoid muscle between the clavicle and the anterior tragus of the ear. On light microscopy, these cysts are, in the vast majority of cases, lined by stratified squamous epithelium, with less frequent contributions by ciliated, respiratory-type epithelium. The subepithelial zone is typically occupied by lymphoid tissue, often with prominent (reactive) germinal centres.[3]

For over a century and a quarter, head and neck surgeons have both defended and attacked the notion of a squamous carcinoma arising in a pre-existing branchial cleft cyst.[4–20] This is more than a mere academic debate, as treatment of a localised carcinoma arising within a developmental cyst and still entirely confined within that cyst would differ from treatment of a metastatic deposit derived from a (presumably occult) head and neck primary tumour situated elsewhere.

As an aside, it is interesting to note that malignant lateral cervical cysts can be related to metastatic thyroid tumours or, more rarely, to primary thyroid carcinoma arising in branchial cleft cysts.[21,22] As with presumed branchiogenic tumours, it is important to evaluate whether such a tumour is a metastasis or a papillary thyroid carcinoma arising in ectopic thyroid tissue in a branchial cleft cyst, as the thyroid gland is derived in part from the two fourth branchial pouches. Immunohistochemical stains for thyroid transcription factor one, p63 and thyroglobulin have proven to be very useful tools to determine the differential diagnosis in such circumstances.[21,22]

Historical perspective

The notion of a squamous carcinoma arising in the setting of a pre-existing developmental lesion – a

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branchial cleft cyst – was first advanced in the latter years of the nineteenth century.[4] Even these early reports warned about the possibility of an occult primary tumour elsewhere. At that time, important differential diagnostic possibilities included 'lymphosarcoma, tuberculous lymphoma, and actinomycosis'.[5] A diagnosis of branchiogenic carcinoma was not routinely made pre-operatively, but, rather, only after surgery or at post-mortem examination. The concept of primary branchiogenic carcinoma gained popularity at the turn of the nineteenth century, and became a well established doctrine.[5,6] Even in the early decades of the twentieth century, it was recognised that major salivary glands, the upper aerodigestive tract, and even the oesophagus and stomach might give rise to cervical metastases which could mimic primary branchiogenic carcinoma.

It was with the 1944 and 1950 publications of Martin and colleagues that real opposition to this theory was aired, as well as opposition to the uncritical acceptance of the notion of primary branchiogenic carcinoma in many cases of cystic squamous carcinoma masses.[7,8] These authors proposed that the diagnostic criteria for primary branchiogenic carcinoma be tightened, and suggested that four criteria be met before a diagnosis of branchiogenic carcinoma could be made unreservedly: (1) the tumour must lie along the anterior border of the sternocleidomastoid muscle; (2) light microscopy must suggest that the tumour originates from a tissue type which is normally found within vestigial branchial apparatus structures; (3) no other primary tumour should be diagnosed during the five years following the putative diagnosis of a branchiogenic carcinoma; and (4) light microscopy must demonstrate that the malignancy has developed within the wall of an epithelial-lined cyst.[7,8] These papers proved to be influential, as in the latter half of the twentieth century the number of reported cases of branchiogenic carcinoma dropped substantially.

The modern debate

Some authors have adopted a deeply sceptical position and asserted that, even in the absence of a detectable primary tumour, cystic cervical deposits of squamous carcinoma will ultimately usually prove to be metastatic tumours.[9,10,12,16–19,23] These authors cite the fact that the original diagnostic criteria for branchiogenic carcinoma were incomplete, due to the absence of panendoscopy and tonsillar biopsy, limited follow up in several instances, and the administration of radiation therapy in many cases (which might have eradicated occult primary tumours and so created the impression of a true primary cervical neoplasm).[9,12]

In a review of 121 adult patients who presented with an initial diagnosis of lateral cervical cysts, Gourin and Johnson[24] demonstrated histological evidence of metastatic squamous cell carcinoma in 12 resected cysts (9.9 per cent). The incidence of malignancy was significantly greater in patients older than 40 years (23.5 per cent). When pre-operative fine needle aspiration or frozen section histological examination showed malignancy, then panendoscopy with directed biopsies of Waldeyer's ring revealed an occult primary tumour in five of these patients.

It has been suggested that patients with a cystic mass located at cervical levels II or III and who are aged 40 years or older should all be investigated by computed tomography (CT) and should undergo ipsilateral tonsillectomy, even if the tonsil appears clinically normal.[25,26]

Currently, the majority of patients who present with a neck mass undergo fine needle aspiration biopsy for cytological analysis. Fine needle aspiration cytology (FNAC) may be useful to exclude a cold abscess (i.e. tuberculosis), particularly in developing countries (Figure 1). When solid tissue is aspirated, a diagnosis is likely, but when only fluid is recovered, it is still possible to distinguish a malignant cyst from a benign cyst by the use of imaged cytometry deoxyribonucleic acid analysis, as the former will demonstrate aneuploid and the latter diploid cells.[27] With this information, it is possible to plan appropriate elective treatment for all patients aged 40 years and older.

Other authors, however, are more ready to accept the possibility of malignancy arising in a pre-existing benign developmental cyst (such as a branchiogenic cyst), and thus are less opposed to the idea of a primary branchiogenic carcinoma.[13–15,20,28–30]

The question remains, who is correct?

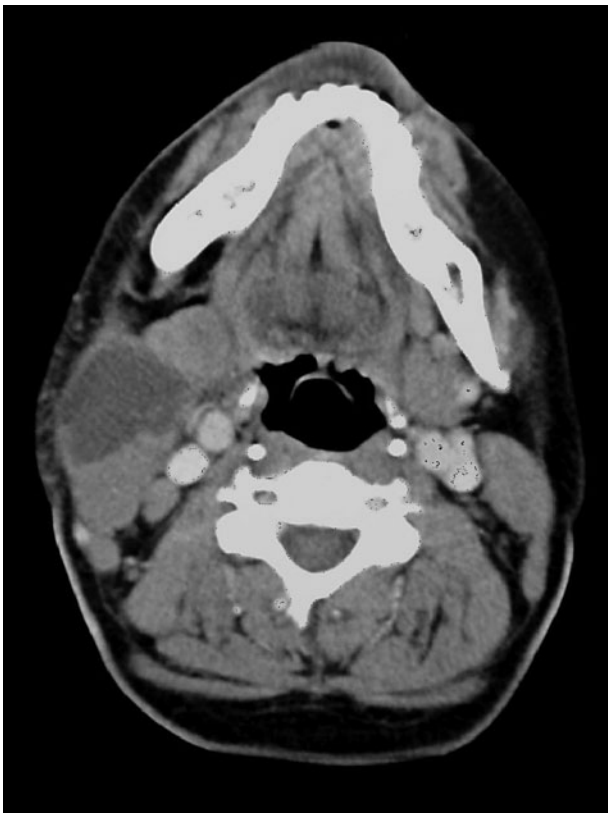

FIG. 1

Cold abscess (tuberculosis) can be confused with other cystic masses, particularly in developing countries.

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Recommendations

Cystic lateral cervical masses in adults over the age of 40 years are presumed to be malignant until proven otherwise.[31] While adjunctive studies (including imaging and FNAC) are of some use, the fact remains – as was observed over a century ago – that surgical excision is usually the best modality to discriminate between benign and malignant cystic neck masses in this age group. Branchiogenic carcinoma is a diagnosis of exclusion. All adult patients over the age of 40 years who present with malignant cervical masses (arising in anatomical regions where branchial cleft anomalies are known to develop) should be assumed to have occult primary tumours. A diagnosis of primary branchiogenic carcinoma should be viewed at the outset with a more than healthy dose of scepticism. The diagnosis of a cystic squamous cell carcinoma in the neck should trigger a search for a presumed primary tumour, both by imaging modalities and by panendoscopy of the upper aerodigestive tract with liberal use of directed biopsies: in particular of Waldeyer's ring. Some would suggest that bilateral tonsillectomies be performed and the tonsils thoroughly examined pathologically before a diagnosis of branchiogenic carcinoma can be considered.[9,10,32]

The authors believe that a cautious approach to a possible prospective diagnosis of branchiogenic carcinoma should consist of the following.

First, the cystic neck mass should be demonstrated to indeed be a cystic squamous carcinoma; this may require imaging, FNAC or surgical biopsy. While malignancy can be diagnosed on cytology, it is only by surgical excision and thorough pathological examination that light microscopic features supportive of a diagnosis of branchiogenic carcinoma can be elicited.

Second, imaging of the head and neck by CT and magnetic resonance imaging should be employed to exclude an occult primary tumour. Some would even add positron emission studies to this stage of evaluation.[33,34]

Third, the patient should undergo panendoscopy with liberal use of directed biopsies, in the absence of detectable pathology (patients in whom panendoscopy reveals clinically suspicious areas should undergo targeted biopsy).

Fourth, bilateral tonsillectomy should routinely be performed. In those patients whose tonsils have been excised previously, the tonsillar beds should be biopsied.

Finally, if all the preceding examinations are negative, then surgical excision of the cervical mass should provide definitive pathological evidence of both a pre-existing benign developmental cyst and a malignant tumour arising therein.

In those patients in whom (against the odds) a diagnosis of primary branchiogenic carcinoma appears possible, the generally recommended treatment is rather aggressive. Wide resection of the tumour itself (with clear margins, if technically possible) should be followed by modified radical neck dissection. While the use of post-operative radiation therapy is not uniformly recommended by all authors (some suggest awaiting recurrence before resorting to adjuvant radiation therapy), we believe that post-operative radiation therapy should be routinely employed, because these tumours are aggressive in their own right, and the failure to locate another primary tumour does not mean that no occult primary tumour exists. Thus, irradiation may serve the twin purposes of treating the neck as well as the (undetected) true primary site.[12,13] The role of adjuvant chemotherapy remains to be settled, although some have advocated its use.[35]

Conclusion

In summary, and to answer the title of this article, it is unlikely that one will encounter and treat a true branchiogenic carcinoma. Certainly, one should entertain this diagnosis, but only following a process of exclusion, and only after a thorough search for evidence of an occult primary carcinoma.

References

1 Benson MT, Dalen K, Mancuso AA, Kerr HH, Cacciarelli AA, Mafee MF. Congenital anomalies of the branchial apparatus: embryology and pathologic anatomy. *Radiographics* 1992;**12**:943–60
2 Golledge J, Ellis H. The aetiology of lateral cervical (branchial) cysts: past and present theories. *J Laryngol Otol* 1994;**108**:653–9
3 Koeller KK, Alamo L, Adair CF, Smirniotopoulos JG. Congenital cystic masses of the neck: radiologic-pathologic correlation. *Radiographics* 1999;**19**:121–46
4 von Volkmann R. The deep branchiogenic carcinoma of the neck. [in German]. *Zentralbl Chir* 1882;**9**:49–51
5 Warner F. Branchiogenic carcinoma. *Ann Surg* 1916; **64**:1–7
6 Crile G, Kearns JE. Branchial carcinoma. *Surg Gynecol Obstet* 1935;**60**:703–9
7 Martin H, Morfit HM. Cervical lymph node metastasis as the first symptom of cancer. *Surg Gynecol Obstet* 1944;**78**: 133–59
8 Martin H, Morfit HM, Ehrlich H. The case for branchiogenic cancer (malignant branchioma). *Ann Surg* 1950; **132**:867–87
9 Micheau C, Klijanienko J, Luboinski B, Richard J. So-called branchiogenic carcinoma is actually cystic metastases in the neck from a tonsillar primary. *Laryngoscope* 1990;**100**:878–83
10 Soh LBK. Branchiogenic carcinomas: do they exist? *J R Coll Surg Edinb* 1998;**43**:1–5
11 Briggs RD, Pou AM, Schnadig VJ. Cystic metastasis versus branchial cleft carcinoma: a diagnostic challenge. *Laryngoscope* 2002;**112**:1010–14
12 Jereczek-Fossa BA, Casadio C, Jassem J, Luzzatto F, Viale G, Bruschini R *et al.* Branchiogenic carcinoma – conceptual or true clinicopathological entity? *Cancer Treat Rev* 2005;**31**: 106–14
13 Khafif RA, Prichep R, Minkowitz S. Primary branchiogenic carcinoma. *Head Neck* 1989;**11**:153–63
14 Lin Y-C, Fang S-Y, Huang R-H. Branchiogenic squamous cell carcinoma: a case report. *Int J Oral Maxillofac Surg* 2004;**33**:209–12
15 Skoulakis CE, Karametos IG, Fericean AA, Kostis JG, Divani S, Valagiannis DE. Branchiogenic squamous cell carcinoma: a case report. *Case Rep Clin Pract Rev* 2006;**7**: 114–18
16 Maturo SC, Michaelson PG, Faulkner JA. Primary branchiogenic carcinoma: the confusion continues. *Am J Otolaryngol* 2007;**28**:25–7
17 Compagno J, Hyams VJ, Safavian M. Does branchiogenic carcinoma really exist? *Arch Pathol Lab Med* 1976;**100**: 311–14

18 Granström G, Edström S. The relationship between cervical cysts and tonsillar carcinoma in adults. *J Oral Maxillofac Surg* 1989;**47**:16–20
19 Thompson LD, Heffner DK. The clinical importance of cystic squamous cell carcinomas in the neck: a study of 136 cases. *Cancer* 1998;**82**:944–56
20 Girvigian MR, Rechdouni AK, Zeger GD, Segall H, Rice DH, Petrovich Z. Squamous cell carcinoma arising in a second branchial cleft cyst. *Am J Clin Oncol* 2004; **27**:96–100
21 Lanzafame S, Caltabiano R, Puzzo L, Cappellani A. Thyroid transcription factor 1 (TTF-1) and p63 expression in two primary thyroid papillary carcinomas of branchial cleft cysts. *Virchows Arch* 2006;**449**:129–33
22 Kreft A, Hansen T, Kirkpatrick CJ. Thyroid transcription factor 1 expression in cystic lesions of the neck: an immunohistochemical investigation of thyroglossal duct cysts, branchial cleft cysts and metastatic papillary thyroid cancer. *Virchows Arch* 2005;**447**:9–11
23 Delank KW, Freytag G, Stoll W. Clinical relevance of malignant lateral branchial cyst [in German]. *Laryngorhinootologie* 1992;**71**:611–17
24 Gourin CG, Johnson JT. Incidence of unsuspected metastases in lateral cervical cysts. *Laryngoscope* 2000;**110**: 1637–41
25 Bath AP, Murty GE, Bradley PJ. Branchial cyst – to endoscope or not? *J Laryngol Otol* 1992;**106**:1006–7
26 Flanagan PM, Roland NJ, Jones AS. Cervical node metastases presenting with features of branchial cysts. *J Laryngol Otol* 1994;**108**:1068–71
27 Nordemar S, Högmo A, Lindholm J, Tani E, Sjöström B, Auer G *et al*. The clinical value of image cytometry DNA analysis in distinguishing branchial cleft cysts from cystic metastases of head and neck cancer. *Laryngoscope* 2002;**112**:1983–7
28 Misonou J, Iwabuchi K, Aizawa M, Murakami S. Mucoepidermoid carcinoma arising in a lymphoepithelial cyst – report of a case and review of the literature on branchiogenic carcinoma. *Jpn J Surg* 1989;**19**:474–9
29 Vera Llao R, Bernat Landoni R, Nogués Orpi J, Sandoval Puig M, González Compta X, Dicenta Sousa M. Does branchiogenic carcinoma exist or not? [in Spanish]. *Acta Otorrinolaringol Esp* 1995;**46**:399–401
30 Singh B, Balwally AN, Sundaram K, Har-El G, Krgin B. Branchial cleft cyst carcinoma: myth or reality? *Ann Otol Rhinol Laryngol* 1998;**107**:519–24
31 Cinberg JZ, Silver CE, Molnar JJ, Vogl SE. Cervical cysts: cancer until proven otherwise? *Laryngoscope* 1982;**92**: 27–30
32 Marlowe FI, Goodman RS, Mobini J, Dave U. Cystic metastasis from occult tonsillar primary simulating branchiogenic carcinoma: the case for tonsillectomy as a "grand biopsy." *Laryngoscope* 1984;**94**:833–5
33 Raghavan U, Bradley PJ. Management of cystic cervical metastasis. *Curr Opin Otolaryngol Head Neck Surg* 2003; **11**:124–8
34 Goldenberg D, Sciubba J, Koch WM. Cystic metastasis from head and neck squamous cell cancer: a distinct disease variant? *Head Neck* 2006;**28**:633–8
35 Katori H, Nozawa A, Tsukuda M. Post-operative adjuvant chemoradiotherapy with carboplatin and 5-fluorouracil for primary branchiogenic carcinoma. *J Laryngol Otol* 2005; **119**:467–9

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