Technetium-99m Pertechnetate Salivary Gland Imaging: Its Role in the Diagnosis of Warthin’s Tumor

Case Presentation and Discussion: Gregory S. Weinstein, Robert T. Harvey, Wayne Zimmer, Suat Ter and Abass Alavi

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CASE PRESENTATION

A 74-yr-old male complained of painless swelling in the right parotid area which started several months ago. There was no associated numbness in the area, and he denied facial weakness. Essentially, the mass was asymptomatic. His past medical history was unremarkable and he had no prior surgery. He was not on any medications. He denied allergies. He had smoked tobacco, two packs a day for 55 yr and quit 6 yr prior to the current medical problem. He did not drink alcohol.

Physical examination revealed a well developed man in no acute distress. He had no head and neck abnormalities except for a right-sided 2 x 3-cm parotid mass. A fine needle aspiration was performed during the initial visit.

An MRI scan revealed a large right parotid mass, measuring 3 cm in its greatest dimension within the inferior aspect of the gland. Two other incidental findings were also noted. The first was a right cerebellonette angle tumor, and the second was two enhancing lesions within the cerebellum, both suspicious for metastatic disease. Fine needle aspiration cytology of the parotid mass revealed normal parotid acini and a few oncocytic cells associated with numerous lymphoid cells, consistent with Warthin’s tumor. No evidence of malignancy was found. Because of the incidental detection of masses in the head, it was decided to initiate a workup to locate a primary tumor. In addition, a radionuclide scan to assess the nature of the parotid mass and to confirm its benign nature was also scheduled.

A radionuclide scan of the parotid gland was performed following the intravenous administration of [99mTc]pertechnetate (Fig. 1). A SPECT scan of the head was also obtained as part of this examination. The image revealed an area of increased focal uptake in the right parotid gland, consistent with the patient’s known Warthin’s tumor. No posterior fossa uptake was noted. A chest x-ray revealed a right upper lobe mass, suggesting carcinoma of the lung and chronic obstructive pulmonary disease. At this point, the patient was referred for definitive therapy for metastatic carcinoma of the lung. No further intervention was considered necessary for the parotid mass since it was confirmed to be a benign lesion and did not cause significant discomfort.

DISCUSSION

Pre-operative diagnosis of a Warthin’s tumor is of considerable value in the evaluation of patients with parotid gland swelling. In this case, the benign nature of the parotid tumor allowed the attending physicians to concentrate their efforts on the management of lung cancer. The use of parotid radionuclide scanning with [99mTc]pertechnetate greatly facilitated the pre-operative evaluation of this patient’s presenting complaint.

Technetium-99m-pertechnetate was first used for brain and thyroid scanning in the early 60s (1,2). Its use for parotid gland imaging was realized incidentally while imaging the brain (1,2). Grove and DiChiro were the first to study the salivary glands with [99mTc]pertechnetate (3). Many reports have appeared in the literature substantiating the role of this imaging technique in the management of patients with parotid gland disease and especially with Warthin’s tumor (4–12). We hope to lend additional support for this effective diagnostic study, which may have since lost popularity in favor of fine-needle aspiration.

Warthin’s tumor (papillary cystadenoma lymphomatosum), a benign neoplasm of the major salivary glands (particularly the parotid gland), was described in 1910 by two German physicians, Albrecht and Arzt (13). The first English cases were described as adenomas of heterotopic salivary glands in the preparotid lymph nodes by Nicholson in 1923 (14). This tumor has a varied nomenclature including adenolymphoma, papillary cystadenoma lymphomatosum, lymphomatous adenoma and oncocytoma, but the term Warthin’s tumor has been extensively used to credit Aldred Scott Warthin who published the first two case reports in the American literature in 1929 (15). Warthin’s tumor is the second most common benign parotid tumor (benign mixed tumors are the most common), and classically accounts for 2% of all head and neck tumors and 6%–10% of parotid gland epithelial tumors (4–6,16–20).
There are reports, however, of high incidences, citing 14%, 14.4% and even 24.4% of all parotid tumors (5,16,17).

Warthin's tumor is the most common salivary tumor to be bilateral and multifocal (12,16). Chapnik observed 12% of patients developing more than one lesion, which can manifest as multiple, discrete primary lesions occurring within one parotid gland (4). Numerous other reports have identified a bilateral incidence of 3%–8% of cases, while 4%–12% are multifocal (8,19,21,23). Finkelstein et al. reported a case of Warthin's tumor presenting as multiple bilateral synchronous parotid masses, which is believed to be the third such case in the literature (8). Additionally, Warthin's tumor has a postoperative recurrence rate of 6%–12% (16,23) which may result from a high frequency of undiagnosed multifocal lesions at the time of original surgery (11).

Clinically, Warthin's tumor is very slow growing and may even appear static over many years. It commonly presents as an asymptomatic painless swelling at the lower pole of the parotid gland for many months (8,17,18,21,22). Chapnik reported a range from 3 wk to 10 yr (4). The facial nerve is usually spared, as nearly all cases are benign (8,16). The majority of tumors are 1–3 cm in diameter, well circumscribed, and encapsulated. Fluctuations in tumor size do not appear to occur (4,21,22). Historically, Warthin's tumor has demonstrated a predilection for males, and the literature consistently cites male-to-female ratios of at least 5:1 (4,6,23). However, recent reports have documented changes in the male versus female distribution, with equal incidence in both sexes since the mid 1970s without explanation. Male-to-female ratios of less than 2:1 are quite common (7,18,21,22). Lamelas et al. found that the increasing incidence of Warthin's tumor in women paralleled similar increases in tobacco consumption and lung cancer deaths among women in an age-matched cohort. In this study, 82% of the female patients were smokers. Given that the parotid duct epithelium is in direct continuity with the oral cavity, they postulated that orally inhaled tobacco smoke may play a role in ductal epithelial metaplasia leading to tumor formation (22).

The peak incidence of Warthin's tumor is frequently observed in the sixth and seventh decades (4,5,16,17). As alluded to earlier, the overwhelming majority of Warthin's tumors are benign, and malignant transformation is rare. Carcinomas arising from this tumor have been estimated at 0.3% of all lesions (16).

Grossly, the tumor is round or oval, encircled by a thick capsule. It rarely infiltrates the surrounding gland. The surface is pink-gray in color, smooth or lobulated (17,19). The histologic diagnosis of Warthin's tumor requires the presence of an epithelial parenchyma and a lymphoid stroma, distinguishing it from an oncocytoma (4,5,16,17). The parenchyma is organized in a tubulopapillary-cystic pattern and features epithelial cells with numerous mitochondria, surrounding dilated cystic spaces of secretory material, which is clear, serous, milky, mucoid or chocolate in color (17). The epithelium lining of the cysts is usually a double layer of cells with papillary projections into the cysts. The inner layer consists of tall columnar cells with a dense oxyphilic granular cytoplasm due to an abundance of mitochondria (4,17,19,21). These cellular changes (referred to as oncocytic changes) commonly occur with aging and their significance is not known, though they are implicated in the neoplastic process (4). The outer layer consists of rounded or cuboidal cells. There is wide variation regarding the extent of cyst formation and cyst contents, the degree of epithelial metaplasia, and the proportion of lymphoid stroma to epithelium (4,8,17,21). A basement membrane separates the epithelium and lymphoid stroma, which supports the epithelial parenchyma and has been found to contain germinal centers along with stem cells, lymphocytes, plasma cells, mast cells, histiocytes and macrophages (4,8,17). The origin of lymphoid stroma has been debated, as will be discussed below.

Paralleling the tumor's interesting histologic composition is its histogenesis, which is based on the fact that lymph nodes are contained within the normal mature parotid gland. During development, the salivary tissue of the expected parotid gland intermingles with the neighboring lymphoid tissue of expected lymph nodes. As these tissues mature, they remain in close proximity of the gland. The mature parotid gland is encircled by a capsule, but encapsulation occurs late in development and results in intrusion of lymph nodes into the parotid gland, and invasion of the peri-parotid lymph nodes with salivary duct tissue. Thus, such elements become a diagnostic component of the tumor (4,8,21,23). Neoplastic transformation of the heteropic salivary gland tissue trapped within lymphoid tissue may be responsible for the formation of these tumors (4). This developmental process leads to several observations, most notably, (1) the presence of ductal tissue within lymphoid
tissue; (2) the location of almost all Warthin’s tumors in lymphatic tissue within or adjacent to the parotid gland; and (3) the multifocal nature of the tumor (8,23).

Debate exists over the role of the lymphoid tissue in this tumor.

Some believe it is a cellular response to epithelial neoplasia, and others believe it is a normal lymph node surrounded by epithelial proliferation. Studies have demonstrated that both T and B lymphocytes are contained within the lymphoid stroma, which may indicate that the tumor may have originated in pre-existing lymph nodes. Others have found functional germinal centers and an abundance of IgA plasma cells in Warthin’s tumors, suggesting an immune response to the tumor. It has also been shown that most Warthin’s tumors have excessive amounts of lymphoid tissue compared to normal lymph nodes. Nonetheless, most authors believe that the majority of Warthin’s tumors develop from heterotopic salivary ducts within pre-existing lymphoid tissue, which undergoes subsequent reactive changes in response to the neoplastic epithelium (4,21). In contrast, the submandibular and sublingual glands develop independently of lymphoid tissue, and are encapsulated early. Their developmental process precludes intermingling of salivary and lymphoid tissues, thus limiting Warthin’s tumor to the parotid gland and its immediate environment (17).

Diagnosis of Warthin’s tumor based on clinical assessment is questionable since the tumor is indistinguishable from other benign lesions of the parotid gland (17). A variety of tissue analyses and imaging techniques have been employed in an attempt to arrive at the correct diagnosis, and such methods include plain radiographs, sialography, [99mTc]pertechnetate scanning and tissue biopsy.

Sialography is useful for evaluating the ducts and parenchyma of the parotid glands, which also may suggest the presence of a tumor as evidenced by displaying the effects on the ductal system (stretching and displacement without duct destruction) (4,5,21). Since this finding is common among all benign parotid gland neoplasms, its presence is not specified as Warthin’s tumor. Malignant tumors more commonly show invasion and destruction of the ducts (5). Thus, the study is limited and therefore should not play a major diagnostic role in this regard (4,17). The combination of sialography and CT scanning may be more reliable than sialography alone in identifying small tumors, determining location of tumor, assessing invasiveness and identifying intrinsic and extrinsic lesions (4,19). This analysis can be further enhanced with the adjunctive use of intravenous administration of contrast, particularly if the lesion is a vascular tumor (4).

Controversy surrounds the use of needle biopsy and aspiration of salivary gland lesions. Needle biopsy is useful in that a tissue specimen is procured upon which a histologic diagnosis may be conferred. If a Warthin’s tumor is identified, surgery may be avoided in high-risk patients or the surgical approach may be tailored for adequate resection of the mass thus sparing neighboring structures (e.g., the facial nerve). However, this procedure also has some limitations in that the specimen may not be representative of the actual lesion and therefore an error in diagnosis may be made (4). Additionally, the facial nerve may be injured during aspiration of a parotid gland mass. Lindberg and Akerman have reported that fine-needle aspiration cytology can be used to achieve a positive preoperative diagnosis in 81% of specimens, while yielding 8% false-negative results (24). Their false-negative rate was reduced to under 5% when the biopsy and cytology were performed by experienced individuals. An 11% nondiagnostic rate could not be reduced because of the cystic nature of the tumor (24). X-ray studies (plain films and CT scans) provide some diagnostic information (e.g., size of lesion, extension, etc.), but lack detailed analysis (e.g., cystic or solid). Radiouclide imaging with [99mTc]pertechnetate has been shown to provide some useful specific information about certain disorders, and can also reflect alterations in normal physiological function (5).

Radiouclide scanning with [99mTc]pertechnetate is a simple and noninvasive method for assessing salivary gland function. It is a suitable radioactive tracer for human use because of its short half-life of 6 hr and pure gamma emission of 140 keV, which is readily detected by a gamma camera (4). The technique is well described in the literature (4,5,10) and involves imaging of the parotid gland in the posterior projection after the intravenous infusion of 5 mCi of the tracer at 60-sec intervals for 20 min and obtaining final images of the patient in water, right lateral and left lateral positions, followed by washout images obtained 3 min after stimulation with orally administered lemon juice to determine adequacy and symmetry of glandular secretion (6).

Salivary imaging with a gamma camera interfaced to a computer allows rapid sequential images and assessment of the three distinct phases: blood flow (uptake), functional (concentration and storage) and washout (drainage of the tracer) (4,5). The activity is compared with the normal tissue surrounding the lesion during these phases, and one of three patterns is noted: "cold," "warm," or "hot." A scan is cold if the lesion does not concentrate [99mTc]pertechnetate as much as the normal gland. A scan is warm if the uptake is similar between the lesion and the normal tissue. A scan is hot if the lesion displays increased [99mTc]pertechnetate uptake (4).

Neoplasms and inflammatory lesions are distinguished from avascular lesions (e.g., cysts), and glandular atrophy based on the activity in the initial blood flow phase: Blood flow is increased in the former, and decreased in the latter group. The functional phase is analyzed for increased or decreased function: Nonfunctioning lesions are usually suggestive of carcinoma, mixed tumors or cysts, whereas hyperfunctioning intrinsic lesions frequently represent Warthin’s tumors. Oncocytomas which are ectopically located are also functional. A normal washout phase is characterized by accumulation of radioactivity within the oral cavity following a secretory stimulus. Delays in this drain-
age pattern may result from obstructed glands, whereas local retention within the gland is strongly supportive of a Warthin’s tumor. This pattern is quite typically seen with Warthin’s tumor because the tumor is capable of concentrating the tracer, but cannot secrete it since the tumor does not communicate with the gland’s ductal system (4,5).

Classically, two parotid neoplasms yield a hot \[^{99m}Tc\] pertechnetate scan; Warthin’s tumor and oncocytoma. Some pleomorphic adenomas can appear with mildly increased uptake of \[^{99m}Tc\] pertechnetate, but the remaining benign tumors do not (4,6,11). However, Abramson et al. found that only the Warthin’s tumor was able to produce a truly hot scan (25). The increased uptake of \[^{99m}Tc\] pertechnetate by Warthin’s tumor and oncocytomas is due to epithelium contained within these tumors which can extract large anions from the blood (such as pertechnetate). There is, however, a subtle difference in the way the Warthin’s tumor and the oncocytoma concentrate \[^{99m}Tc\] pertechnetate. An oncocytoma concentrates the radionuclide within the proper tumor cells, whereas a Warthin’s tumor will concentrate the radionuclide within the tumor mass and thus will not demonstrate a cavitary appearance as might the former (4). Additionally, multifocality does not occur with oncocytoma, which may help in the differentiation of these two similar tumors (9), but this has been disputed (4).

As stated, Warthin’s tumor does not communicate with the ductal system, allowing the accumulated \[^{99m}Tc\] pertechnetate to remain in the gland without being secreted. Therefore, the washout images are very important in diagnosing Warthin’s tumor, because this tumor is not capable of secreting the tracer whereas both normal parotid gland and most other parotid abnormalities drain upon stimulation. Thus, a washout pattern that shows unchanged or even increased pattern of activity is quite unique for Warthin’s tumor (6).

Several authors have reported success with \[^{99m}Tc\] pertechnetate scanning. Chapnik noted 10/10 patients with Warthin’s tumor to have a positive scan (4). Ellledge and Moss found the scan very predictive in their series of 23 patients with Warthin’s tumor (7). Higashi et al. (6) and Liu et al. (9) also reported success in 5/5 and 4/4 patients with Warthin’s tumors, respectively. Sostre et al. found that the washout scan successfully identified Warthin’s tumors in 9/9 patients (12). Despite this widespread success with radionuclide scanning, there are reports which dispute its routine application, claiming that salivary gland imaging lacks sensitivity and can detect only clinically apparent mass lesions; \[^{99m}Tc\] pertechnetate scanning is nonspecific for Warthin’s tumor; salivary gland function is incompletely understood; and protocols for salivary gland imaging are cumbersome and often discourage nuclear medicine laboratories from carrying out such studies (10).

False-positive scans indicating poor specificity have been reported. Not all hot nodules are Warthin’s tumors (4,6,10,19). False-positive scans may result from partial obstruction of the parotid gland, or from stasis or pooling of secretions within dilated acini and ducts as in Sjogren’s syndrome. Additionally, a normal gland could be interpreted as a hot gland if the contralateral parotid gland is nonfunctioning (4). Acute parotitis was also found to mimic Warthin’s tumor in that both produced a hot uptake scan. However, the two conditions differed in the washout scans, again reinforcing the importance of performing the final phase in order to detect Warthin’s tumor (9).

False-negative scans indicating a lack of sensitivity have also been reported (4). Not all Warthin’s tumors actively concentrate \[^{99m}Tc\] pertechnetate to a higher level than the surrounding normal tissue. In this instance, the washout phase assumes even greater importance in detecting a tumor since the tracer will wash out of normal parotid tissue (5). Additionally, some Warthin’s tumors will display a mixed washout pattern as has been defined by Sostre et al.: homogeneous (evenly hot), nonhomogeneous (alternating hot and warm areas) and mixed (hot and cold areas). The classic homogeneously hot pattern was seen in 44% of patients. Nonhomogenous and mixed lesions were found in 22% and 33% of patients, respectively. These latter scan patterns resulted from cystic inclusions within the tumor mass. Large cysts produced a mixed scan pattern and multiple small cysts produced a nonhomogeneous pattern. In contrast, those patients with a homogeneous pattern had mucoid or mucopurulent material within the tumor and noticeably lacked cystic formation (12). Mishkin indicates that patients with focal swellings (inflammatory or metastatic foci, cysts and abscesses involving the glands) may not benefit from radionuclide scanning since they are nonfunctioning (10). Radionuclide scanning however, may be able to determine the underlying cause in diffuse parotid gland swellings, which includes parotitis, functional or mechanical obstruction due to major duct occlusion or duct abnormalities, as well as infiltration of the lobules by lymphocytes. He stated that \[^{99m}Tc\] pertechnetate scanning offers an excellent functional image of the salivary glands, but is not always specific for Warthin’s tumor and interpretation of a scan relies on human judgment (10).

CONCLUSION

Surgery is considered curative in the management of patients with Warthin’s tumor. Since the tumor is usually well-defined and superficial, its removal is easily achieved. However, if incompletely removed, or if detected foci remain after the original surgery, tumor recurrence is expected (5,17). Approaches to the removal are based on tumor size and location, and include limited resection, superficial and deep lobe parotidectomy. Usually, the facial nerve is spared (4). The literature has shown, as has this report, that tumor assessment can be enhanced by performing \[^{99m}Tc\] pertechnetate radionuclide scanning. From a surgical perspective, these scans are extremely useful. Greyson and Noyek firmly believed that the preoperative diagnosis of a functional parotid gland tumor
indicates a Warthin’s tumor, and given its benign nature, a less aggressive surgical approach would be indicated (5). Frequently, patients who are in the sixth and seventh decades of life have confounding medical problems, and may not be able to tolerate the rigors of surgery. It would be unjust to remove a parotid gland mass in these patients, only to discover that it was a benign tumor. We believe that such a scenario could be avoided with the use of $[^{99m}Tc]$ pertechnetate scanning. Clearly it would be more appropriate in such instances to periodically monitor the tumor’s course and behavior.

The combination of a fine-needle aspiration indicative of Warthin’s tumor plus a radionuclide scan virtually confirms the presence of a benign Warthin’s tumor. This is diagnostically acceptable and allows the surgeon to then make a sound decision and to avoid surgery in patients in whom it is safe to follow these slow-growing tumors. An elderly patient of 70 yr with a 3-cm mass in the parotid gland can easily be followed for the remainder of his life if surgery is precluded for other reasons. Therefore, it behooves the surgeon and the nuclear medicine physician to work together to provide the most sound approach in patients with suspected Warthin’s tumors.

REFERENCES