EUR. J. ONCOL.; Vol. 21, n. 3, pp. 185-189, 2016

Sweat gland adenocarcinoma with high serum levels of CA19-9 and CEA: difficulty in diagnosis and treatment

Jungmyung Park[1], Se-Il Go[1*], Myoung Hee Kang[1*], Won Sup Lee[1], Min Jeong Lee[1], Moon Jin Kim[1], Hoon-Gu Kim[1], Dong Chul Kim[2], Jeong-Hee Lee[2], Gyung Hyuck Ko[2]*

[1] Department of Internal Medicine, Institute of Health Sciences, Gyeongsang National University School of Medicine, Jinju, Korea; [2]Department of Pathology, Institute of Health Sciences, Gyeongsang National University School of Medicine, Jinju, Korea

Summary. Sweat gland adenocarcinoma is a rare form of adenocarcinoma of the skin. Its occurrence has been reported mainly on the scalp, upper extremities, or upper trunk. Even though it metastasizes to other major organs, we may not have difficulty in differentiating between primary lesions and metastatic lesions. Here, we will describe a 70-year-old Korean man with a diagnosis of adenocarcinoma accompanying high serum levels of CA 19-9 and CEA. PET-CT revealed multiple high glucose uptake lesions in the pancreas, lung, and submandibular gland. The final diagnosis was high grade eccrine ductal adenocarcinoma (type III) in sweat gland adenocarcinoma. The clinical course of this case was very aggressive in contrast to previously reported cases where sweat gland adenocarcinoma had a long indolent clinical course. This patient succumbed to disease progression 3 months after diagnosis.

Key words: sweat gland neoplasm, CA 19-9, CEA, Eccrine ductal adenocarcinoma

Introduction

Malignant sweat gland adenocarcinoma is a rare neoplasm with high recurrence and variying prognosis (1-3). This neoplasm is often not clearly diagnosed or encountered as an unexpected histologic diagnosis (1). Its occurrence has been reported mainly on the scalp, upper extremities, or trunk above the nipple line. The scalp is the most common clinical site though it often spreads to the lymph nodes. The liver, lungs and bones are the most common metastatic sites (1). The treatment of choice is wide surgical excision. The role of adjuvant chemotherapy and radiotherapy is not clearly established (1, 3).

We here report an unusual case of sweat gland adenocarcinoma showing high serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) which have been used as the tumor markers for prediction of recurrence and prognosis of patients with adenocarcinoma such as pancreatic, lung, and hepatobiliary cancer (4-6). These findings suggested that the primary lesion may be the pancreas or lung. In addition, the clinical course of this case was very aggressive in contrast to reported cases where sweat gland adenocarcinoma progressed slowly (7).We therefore need to review the clinical findings and histology meticulously. Here, this rare case is fully discussed including diagnosis and clinical course, with a review of the literature.

* Contributed equally

Case report

A 70-year-old Korean male without any underlying diseases visited a local clinic because of a nodular lesion on the scalp which persisted for 1 month (Figure 1). He underwent biopsy for routine histopathological examination, and it was diagnosed as adenocarcinoma. He was then admitted to our hospital for further evaluation and management.

His vital signs were stable upon admission. Physical examination revealed a 2 cm-sized central ulcerative erythematous nodular lesion on the scalp, a 2.5 cm mobile palpable lymph node on the left side of the neck, and a 2 × 3 cm hard subcutaneous mass on his back.

On admission, the complete blood count (CBC) was within the normal range. Biochemical tests revealed that sodium and chloride levels were reduced to 130.8 mmol/L and 87.3 mmol/L, respectively. Other findings were within the normal range. In a tumor marker test, the level of serum CEA and CA 19-9 levels proved to have increased to 20.32 ng/mL and 8391.00 U/mL, respectively. Other findings were within the normal range. PET-CT revealed hot spot lesions in the pancreas, the right lung, the subcutaneous area, the right submandibular gland, and the bone (thoracic vertebrae) (Figure 2).

Microscopically, the epidermis was intact. The tumor arising from an adnexal structure invaded the surrounding dermis with a nesting pattern in the dermis. The tumor nests had an irregular shape with no basal layer. The tumor was an adenocarcinoma with tubules, cribriform and displaying a cord arrangement. Some lumens contained secretion. The tumor cells were composed of atypical cuboidal cells with pleomorphism and an abnormal chromatin pattern. The nuclei were hyperchromatic and had occasionally nucleoli (Figure 3).

After diagnosis, we started chemoradiation (total 25 Gy and 5 Gy daily schedule) with floxuridine for 3 weeks to control the metastatic lesion to the thoracic vertebrae and avoid cord compression. 3-week chemoradiation failed to bring any clinical benefit: grade 2 general weakness developed 1 week after completion of treatment. He then received palliative care in the outpatients clinic. The patient died of disease progression 3 months after the initial diagnosis.

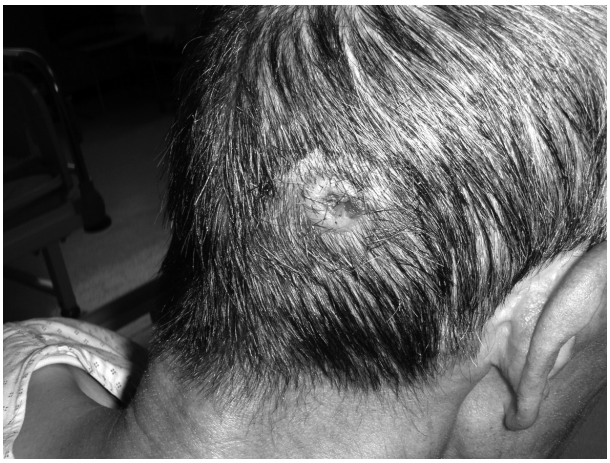

Figure 1. Gross findings showing metastases. A 2-3 cm sized reddish ulcerative crater-like lesion on the scalpclimate (From IMO website: http://www.irimo.ir).

Discussion

Sweat gland carcinomas are rare neoplasms, predominating between 50-90 years of age (8). It is an unexpected histological diagnosis because of its rarity and the variety of clinical courses (1). In 1951, Stout *et al.* suggested restricting the name "sweat gland carcinoma" to "glandular, anaplastic, and infiltrating neoplasms" to distinguish it from encapsulated cystic sweat gland neoplasms (9). Miller, in 1967, stressed the need to focus the diagnosis of this tumor according to its aggressive characteristics: local recurrence, metastasis, or histologic evidence of anaplastic features and infiltrating growth (10). This case displayed aggressive clinical features and histological evidence of infiltrating growth even though the anaplastic feature was not prominent. In 1971, El-domeiri *et al.* subdivided this neoplasm histologically into 5 types (low grade differentiated I, low grade undifferentiated II, high grade differentiated III, high grade undifferentiated IV, and anaplastic small cell V) (7). This case was categorized as high grade (III) eccrine ductal adenocarcinoma. In 1997, Ashley *et al*. suggested that microscopic findings of sweat gland carcinoma should reveal cellular pleomorphism, tumoral cell networks and islets, irregular nuclei and abnormal chromatin patterns, high rates of mitosis, and deep structure invasion (11). This case was consistent with such a pathological description in that

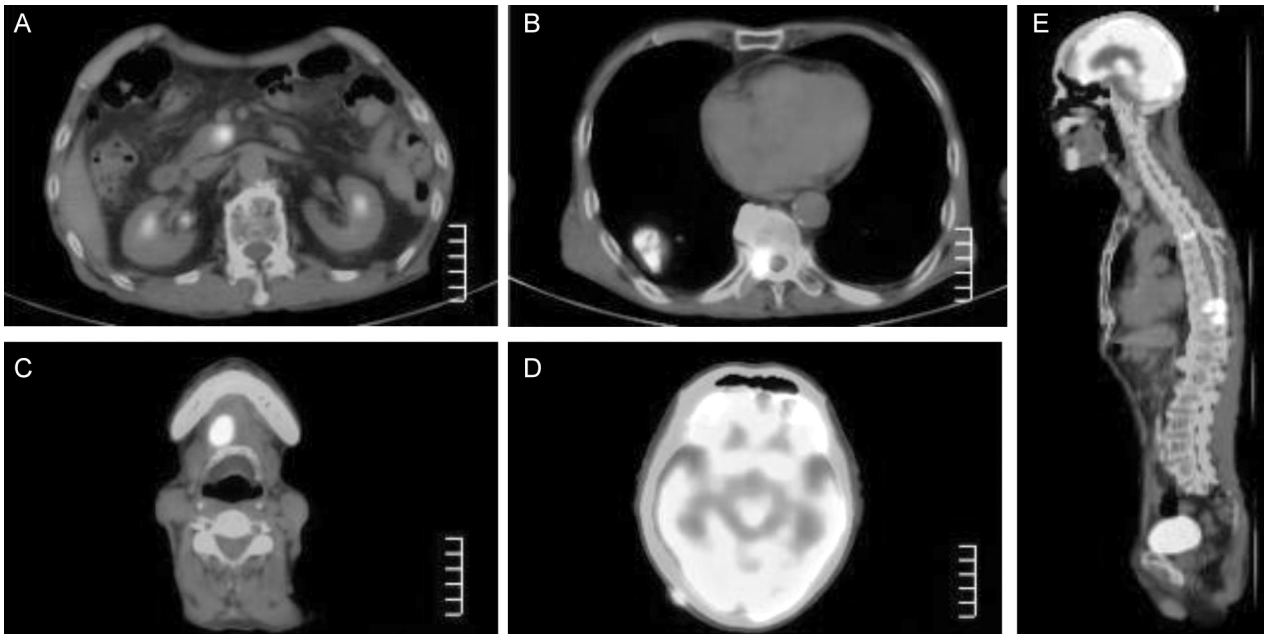

Figure 2. Whole body PET-CT. A. Parenchymal organs; pancreas, body (mSUV 4.91). B. Right lower lung (mSUV 6.19). C. Right submandibular (mSUV 3.37). D. Bones; skull (mSUV 6.96 at the highest). E. T4, 9, 10, sacrum (mSUV 6.12 at the highest).

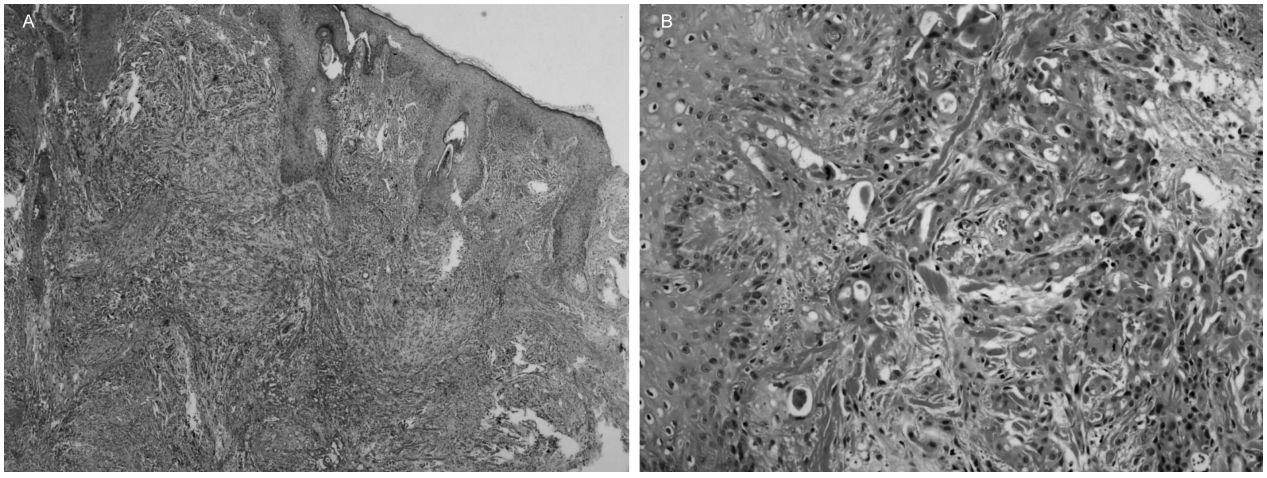

Figure 3. Representative features with H&E staining. A. Epidermis is intact. The tumor arises from an adnexal structure in the dermis and invades the surrounding dermis with a nesting pattern (x40). B. The tumor is an adenocarcinoma with tubules. Some lumens contain secretion. The tumor cells are composed of atypical cuboidal cells with pleomorphism and an abnormal chromatin pattern. The nuclei are hyperchromatic and occasionally have nucleoli (x200).

it showed cellular pleomorphism, abnormal chromatin patterns, and deep structure invasion.

El-Domeiri *et al.* mapped the anatomical distribution of 83 cases (7). Head, upper extremities, or trunk above the nipple line were the most frequent sites of the primary lesion (12). Metastases are frequent and occur mainly in regional nodes, as well as the skin (2, 13). Usually, the tumor is non-tender, aver-

ages 1.5 cm in its longest dimension, is ulcerated and/or surrounded by telangiectases (12). Previous reports have suggested that a violaceous color is typical of this type of tumor (9, 14). However, in our case the size of the cutaneous lesion was larger than average, and of normal colour, in accordance with other reports that the color of the skin nodule is not characteristic for sweat gland carcinoma (9, 12, 14, 15). In addition, this case had another subcutaneous nodule as well as other lesions in visceral organs: the pancreas and the submandibular gland to which sweat gland carcinoma does not frequently metastasize. However, it is often observed that advanced adenocarcinoma of another primary origin (the lung and the pancreas) also metastasizes to the skin including the scalp (16). Theoretically, a long-standing advanced sweat gland carcinoma can metastasize near to the skin, but in this case another subcutaneous lesion was found on the back far from the scalp. Furthermore, the patient noticed the scalp lesion just 1 month before diagnosis, which ruled out lung cancer or pancreatic cancer. The pathologist considered it a ductal eccrine carcinoma on the basis of the clinical information, and the preserved eccrine gland features typical of the sweat gland though with rare mitosis.

Some debate might still be open as to the multimodal manifestation of real sweat gland carcinoma: ductal eccrine-like carcinoma may, in fact, develop in pancreatic and lung cancer due to identical gland morphogenesis. The second reason is that this case had elevated serum levels of CA19-9 as well as CEA which are classic tumor markers for pancreatic, lung, and hepatobiliary cancer (17). CEA consists of glycosyl phosphatidyl inositol (GPI) cell surface-anchored glycoproteins involved in cell adhesion. It serves as L-selectin and E-selectin ligands, which may be critical to the metastatic dissemination of colon carcinoma cells (18). CEA is normally produced in gastrointestinal tissue during fetal development, but the production stops after birth. Thus, CEA is usually present at very low levels in the blood of healthy adults. However, the serum levels are raised in some types of cancer: CEA may be elevated in the blood of some people with cancer of the pancreas, breast, biliary, or lung as well as colorectal cancer. For pancreatic masses, CA19-9 can be useful in distinguishing between cancer and other diseases of the gland (19). However, these two biomarkers may also be elevated in non-neoplastic conditions like ulcerative colitis, pancreatitis or cirrhosis (20). However, very high levels (> 1,000 U/mL) are rarely observed in non-neoplastic conditions (19). In addition, marked elevation of serum CA19-9 has not yet been reported in sweat gland carcinoma, this being the first such (> 1,000 U/mL) expressed in the normal epithelium of sweat glands (21). Basically CA19-9 serum level is also elevated in other benign lesions (22, 23), hence the serum CA19-9 level is limited to use as a surrogate marker for cancer diagnosis. However, the levels of CA-19-9 are rarely elevated to as much as 1,000 U/mL or higher in benign diseases (22), this being rather more common in malignant ones. The serum level of CEA has also been reported to be elevated in non-neoplastic conditions such as ulcerative colitis, pancreatitis, cirrhosis, COPD, Crohn's disease, as well as in smokers. As with CA19-9, the serum CEA level is rarely elevated to a level of 10 ng/mL or higher in benign diseases (24-26).

A further puzzling clinical condition is that the scalp lesion was detected just one month before diagnosis. The clinical course of this disease appeared different from reported sweat gland carcinomas and similar to other aggressive solid cancers such as pancreatic and lung cancer. It has also been reported that widespread sweat gland carcinoma can be as fatal as that of other aggressive solid cancers (3, 7, 12). However, sweat gland carcinoma generally grows slowly over many years (8, 13, 27). Even in patients with metastatic disease, the course may be prolonged up to 20-30 years (12). This case showed widespread metastatic lesions at diagnosis and rapid progression, resulting in only 3-month survival after the initial diagnosis.

In the discussion, we found that one interesting point, the relation between the clinical behavior of the sweat gland and high levels of CA19-9 and CEA. CEA has actually been used as a prognostic marker in lung and colorectal cancers (4, 17), and appears to be involved in cancer progression and metastasis (18). Thus it seems that sweat gland carcinoma producing high CA19-9 and CEA may have a more aggressive clinical course than other sweat gland carcinomas.

Acknowledgments

This study was in part supported by a grant from the Korean Cancer Research Institute.

References

1. Chintamani, Sharma R, Badran R, *et al.* Metastatic sweat gland adenocarcinoma: A clinico-pathological dilemma. World J Surg Oncol 2003; 1 (1): 13.
2. Lee JS, Chang KC, Chen HH, *et al.* Malignant sweat gland tumor presenting as an unusual dural-based lesion: case report. J Neurooncol 2010; 99 (2): 273-6.
3. Bahl A, Sharma DN, Julka PK, *et al.* Sweat gland carcinoma with lung metastases. J Cancer Res Ther 2006; 2 (4): 209-11.
4. Grunnet M, Sorensen JB. Carcinoembryonic antigen (CEA) as tumor marker in lung cancer. Lung Cancer 2012; 76 (2): 138-43.
5. Humphris JL, Chang DK, Johns AL, *et al.* The prognostic and predictive value of serum CA19.9 in pancreatic cancer. Ann Oncol 2012; 23 (7): 1713-22.
6. Patel AH, Harnois DM, Klee GG, *et al.* The utility of CA 19-9 in the diagnoses of cholangiocarcinoma in patients without primary sclerosing cholangitis. Am J Gastroenterol 2000; 95 (1): 204-7.
7. el-Domeiri AA, Brasfield RD, Huvos AG, *et al.* Sweat gland carcinoma: a clinico-pathologic study of 83 patients. Ann Surg 1971; 173 (2): 270-4.
8. Leonhardt FD, Zanoni A, Ponce F, *et al.* Eccrine sweat gland carcinoma. Braz J Otorhinolaryngol 2007; 73 (2): 286.
9. Stout AP, Cooley SG. Carcinoma of sweat glands. Cancer 1951; 4 (3): 521-36.
10. Miller WL. Sweat-gland carcinoma. A clinicopathologic problem. Am J Clin Pathol 1967; 47 (6): 767-80.
11. Ashley I, Smith-Reed M, Chernys A. Sweat gland carcinoma. Case report and review of the literature. Dermatol Surg 1997; 23 (2): 129-33.
12. Hirsh LF, Enterline HT, Rosato EF, *et al.* Sweat gland carcinoma. Ann Surg 1971; 174 (2): 283-6.
13. Panet-Raymond G, Johnson WC. Adenocarcinoma of the eccrine sweat gland. Arch Dermatol 1973; 107 (1): 94-6.
14. Elliott GB, Ramsay DW. Sweat gland carcinoma. Ann Surg 1956; 144 (1): 99-106.
15. Smith CC. Metastasizing carcinoma of the sweat-glands. Br J Surg 1955; 43 (177): 80-4.
16. Schwartz RA. Cutaneous metastatic disease. J Am Acad Dermatol 1995; 33 (2 Pt 1): 161-82; quiz 83-6.
17. Holubec L, Jr., Topolcan O, Pikner R, *et al.* The significance of CEA, CA19-9 and CA72-4 in the detection of colorectal carcinoma recurrence. Anticancer Res 2000; 20 (6D): 5237-44.
18. Thomas SN, Zhu F, Schnaar RL, *et al.* Carcinoembryonic antigen and CD44 variant isoforms cooperate to mediate colon carcinoma cell adhesion to E- and L-selectin in shear flow. J Biol Chem 2008; 283 (23): 15647-55.
19. Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. Eur J Surg Oncol 2007; 33 (3): 266-70.
20. Maestranzi S, Przemioslo R, Mitchell H, *et al.* The effect of benign and malignant liver disease on the tumour markers CA19-9 and CEA. Ann Clin Biochem 1998; 35 (Pt 1): 99-103.
21. Arends JW, Verstynen C, Bosman FT, *et al.* Distribution of monoclonal antibody-defined monosialoganglioside in normal and cancerous human tissues: an immunoperoxidase study. Hybridoma 1983; 2 (2): 219-29.
22. Marrelli D, Caruso S, Pedrazzani C, *et al.* CA19-9 serum levels in obstructive jaundice: clinical value in benign and malignant conditions. Am J Surg 2009; 198 (3): 333-9.
23. Waanders E, van Keimpema L, Brouwer JT, *et al.* Carbohydrate antigen 19-9 is extremely elevated in polycystic liver disease. Liver Int 2009; 29 (9): 1389-95.
24. Bassi C, Salvia R, Gumbs AA, *et al.* The value of standard serum tumor markers in differentiating mucinous from serous cystic tumors of the pancreas: CEA, Ca 19-9, Ca 125, Ca 15-3. Langenbecks Arch Surg 2002; 387 (7-8): 281-5.
25. Shitrit D, Zingerman B, Shitrit AB, *et al.* Diagnostic value of CYFRA 21-1, CEA, CA 19-9, CA 15-3, and CA 125 assays in pleural effusions: analysis of 116 cases and review of the literature. Oncologist 2005; 10 (7): 501-7.
26. Grigorov L, Lutakova E, Chilova B, *et al.* Determination of the level of tumour markers (CA-15-3, CA-125, CA-19-9, NSE, SCC, SP-1, CEA, AEP, ferritin, hCG) in cancer patients undergoing radiotherapy, surgery or a combined therapy. Folia Med (Plovdiv) 1995; 37 (4A Suppl): 47.
27. Morris DM, Sanusi ID, Lanehart WH. Carcinoma of eccrine sweat gland: experience with chemotherapy, autopsy findings in a patient with metastatic eccrine carcinoma, and a review of the literature. J Surg Oncol 1986; 31 (1): 26-30.

Received: 3.12.2013
Accepted: 21.7.2015
Address: Prof. Won Sup Lee, M.D., PhD.,
Institute of Health Sciences, Department of
Internal Medicine, Gyeongsang
National University School of Medicine,
90 Chilam-dong, Jinju, 660-702, South Korea
Tel. 82-55-750-8733;
Fax 82-55-758-9122;
E-mail: lwshmo@hanmail.net or lwshmo@gnu.ac.kr