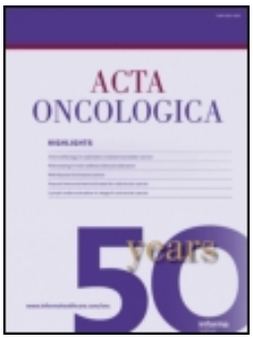

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LETTER TO THE EDITOR

Metastatic granular cell tumor: A case report and review of the literature

SERCAN AKSOY[1], HUSEYIN ABALI[2], SAADETTIN KILICKAP[1], HAKAN HARPUTLUOGLU[1] & MUSTAFA ERMAN[1]

[1]*Hacettepe University Institute of Oncology, Department of Medical Oncology, Ankara, Turkey and* [2]*Ankara Numune Egitim ve Arastirma Hastanesi, Department of Medical Oncology, Ankara, Turkey.*

To the Editor

Granular cell tumors (GCT) are uncommon benign tumors. They may occur in various sites. The tongue and breast comprise the two most common locations, while a lesion in the digestive and respiratory tracts is not unusual. Laryngeal involvement is fairly uncommon and is present in approximately 10% of all cases [1]. Malignant GCTs represent less than 2% of all granular cell tumors [2]. As with their benign counterparts, malignant GCT have a wide anatomic distribution. However, they carry a poor prognosis, with recurrence and metastasis typically within one year of diagnosis [3].

We present a case of malignant granular cell tumor arising from larynx, which has metastasized to lungs and bones. We also conducted a search on the MEDLINE database (National Library of Medicine, Bethesda, MD) and identified 52 previously reported cases of metastatic GCT whose survival data were reported. Basic characteristics of these cases together with ours are described in the following sections. We also review the metastatic GCT in literature.

Case Report

A 43-year-old woman was admitted to the hospital for long-standing cough and recent hemoptysis. In her past history, she had undergone right vertical laryngectomy in another institution two years ago. The diagnosis was laryngeal GCT. Physical examination was unremarkable except for decreased breath sounds in the apex of the right lung. Chest x-ray revealed infiltration of right upper lung region. Computed tomography (CT) of the thorax showed mediastinal lymphadenopathies as well as a lesion that partially obstructed the upper lobe bronchus and invaded the inferior vena cava. Bronchoscopy revealed a bright, smooth and vascularized mass, obstructing the right upper lobe entrance. Punch biopsy was performed. Histopathological examination showed a GCT. The lesion appeared inoperable due to the invasion of large vessels. Ultrasound and CT of the abdomen showed a giant hemangioma in the right lobe of the liver. This finding was confirmed by biopsy. Sixty Gy of external radiotherapy was administered to the pulmonary lesion. This intervention resulted in the palliation of hemoptysis, but the size of the lesion remained stable. As no other effective treatment modality was available, a decision to administer chemotherapy was made. She received three cycles of cisplatin and fluorouracil. Toxicity was acceptable, however, the pulmonary lesion remained unchanged while multiple osteoblastic lesions appeared on direct x-rays and radionuclide bone scan. Chemotherapy was discontinued, and she was given radiotherapy to the right distal femur for pain palliation. Oral etoposide 50 mg/day was prescribed, but patient could not tolerate and refused to use it after only ten days of treatment.

Correspondence: Sercan Aksoy, Hacettepe University Institute of Oncology, 06100, Sihhiye, Ankara, Turkey. Tel: +90 312 3052937. Fax: +90 312 3092905. E-mail: saksoy07@yahoo.com

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Table I. Clinical features of metastatic granular cell tumor cases.

Ref #	Age	Sex	Primary tumor site	Metastases	Treatment modality	DFS	OS
[1]	72	M	Subglottic mass	Lung	S+CT	0	14+
[2]	37	F	Tongue	Local recurrence	S	72	72+
[3]	26	F	Lower leg	Local recurrence	S	24	24+
[3]	18	F	Lower back	Local recurrence	S	12	12+
[3]	36	F	Leg	?		12	12+
[3]	38	F	Buttock	Lymph nodes	S	24	24+
[3]	41	F	Neck	Lymph nodes	S	12	12+
[3]	41	F	Shoulder	Local recurrence, heart, pleura, lung		12	24
[3]	41	F	Groin	Local recurrence, bone, brain	S	12	48
[3]	42	M	Finger	?	S	12	24
[3]	49	M	Chest wall	Local recurrence, lung	S	48	108
[3]	56	F	Vulva	Lymph nodes	S	24	24+
[3]	58	F	Larynx	Local recurrence, distant metastasis	S	24	36
[3]	56	F	Upper Arm	Lung, liver, bone, thyroid	S	24	24
[3]	56	F	Chest wall	Bone, lung	S	12	24
[3]	69	F	Chest wall	Lung	S	48	96
[3]	70	F	Axilla	Local recurrence, lung	S	60	96
[3]		M	Thigh	Lung	S	48	48+
[4]	41	F	Hard palate	Local recurrence	S	54	54+
[5]	?	M	Abdominal wall	Liver, lung	S	?	5
[5]	?	M	Breast	Liver, lung, bone	CT	?	7
[6]	21	F	Retroceacal space	Lung	S	0	7
[7]	72	M	Cervical region	Lymph node, eye, lung, bone	S	24	84
[8]	42	M	Lateral cutaneous nerve	Lung, liver, bone	S+CT	–	6+
[9]	57	F	Pararectal mass	Liver	S	8	11
[10]	55	F	Vulva	Lung, liver, bone	S	4	4
[11]	72	F	Hip	Lung, pleura	Supportive care	0	9
[12]	44	M	Neck	Cervical spinal cord, para-aortic lymph nodes, lungs, kidney and liver	S+RT	36	36+
[13]	30	M	Infratemporal fossa	Local recurrence	S + RT	12	12+
[14]	42	F	Subcutaneous mass in sacrococcygeal area	Local recurrence and lymph node	S	8	52
[15]	43	F	Sciatic nerve	Local recurrence, lung	S	24	38
[16]	52	M	Lower lip	Local recurrence, lymph node, lung	S + RT	24	78
[17]	56	F	Anterior chest wall mass	Breast, lymph node	S	8	8+
[18]	46	F	Breast	Lymph nodes, lungs, liver, and bone	S	?	108+
[19]	60	M	Lower limb	?	S	?	12+
[20]	69	M	Thigh	?	S	?	3
[21]	33	F	Vulva	Lymph nodes	S	6	6+
[22]	60	M	Lumbosacral	Lymph nodes, lungs	S	?	36+
[23]	?	?	Chest wall	Lymph node	S	0	0+
[24]	33	F	Buttock	Local recurrence	S+RT	10	58+
[25]	44	F	Tongue	Tongue, trachea, lung, and mediastinum	S	120	120+
[26]	40	M	Buttock	Local recurrence, lymph node, lungs	S	16	87
[27]	51	F	Subungual tissue of finger	Local recurrence, multiple cutaneous nodules	S+CT +RT	24	42
[28]	41	M	Scapula, subcutaneous tissue	Local recurrence	S	24	24+
[28]	52	M	Pelvis, deep soft tissue	Local recurrence	S	17	17+
[29]	18	M	Anal canal	Local recurrence, inguinal lymph nodes	S+RT	10	24+

Table I (*Continued*)

Ref #	Age	Sex	Primary tumor site	Metastases	Treatment modality	DFS	OS
[30]	48	F	Urinary Bladder	Local recurrence	S	4	40+
[31]	30	F	Bilateral Breast	Right groin	S	36	36+
[31]	36	F	Breast	Vulva	S	36	36+
[32]	21	F	Cutaneous nodule	Local Recurrences	S	4	11+
[33]	32	F	Vulva	Lymph nodes, Lungs	S	?	91
[34]	17	F	Vulva	Lymph nodes	S	?	35+
Current report	43	F	Larynx	Lung, Bone	S +RT + CT	24	48+
	Median 42	**F/M**				**Median**	**Median**
	(17–72)	35/18				17	84

S: Surgery; RT: Radiotherapy; CT: Chemotherapy; F: Female; M: Male.

On her last visit 24 months after the detection of metastatic disease, she is in good health and symptom-free except for mild pain of the right femur that responds well to paracetamol. She has not been given any specific treatment since 12 months.

Discussion

GCT is almost always benign. However, a malignant course is encountered in 2% of cases. Differentiation between benign and malignant GCTs is often difficult, and only the development of metastases may ultimately establish malignancy [3]. Because malignant GCTs are extremely rare, an effort has been made to identify specific features that would predict malignant behavior. Based on the cumulative experience of previous case reports of malignant GCTs, six histologic criteria are considered to be important [4]. These include spindling of the tumor cells, the presence of vesicular nuclei with large nucleoli, increased mitotic rate (>2 mitoses/10 high-power fields at 200× magnification), a high nuclear to cytoplasm ratio, pleomorphism, and necrosis [5]. Histologically, malignant GCT is diagnosed when three or more of the six criteria are fulfilled. In addition to these morphological features, upregulation of p53 as well as Ki-67, a nuclear proliferative marker, has been recently found to correlate with an aggressive clinical course and malignant behavior. In a recent study, p53 immunostaining was negative in all benign cases, while p53 expression was seen in greater than 10% of the cell population in 21 of 25 (79%) malignant GCTs. Similarly, benign GCTs showed immunoreactivity of Ki-67 in 1% or less of the tumor cell population, while fourteen of 25 (56%) malignant tumors had Ki-67 immunoreactivity in up to 30% of the cell population [3]. Clinical characteristics like size larger than 5 cm, multicentricity, rapid growth, and recurrent disease may also increase the likelihood of malignant behavior.

We searched PubMed for metastatic GCT and summarized some clinical characteristics of 53 cases in Table I. Metastatic GCT is more commonly seen in women with a female to male ratio being 2.5:1 (n = 38/15). Patient age at presentation ranges from 17 to 72 with the median age at diagnosis being 43 years.

Almost all patients have been treated surgically at diagnosis. Most metastases develop within two years following diagnosis. Median disease free survival was 17 months (95% confidence interval [CI]: 13–21). Most frequently affected sites are the lungs, liver and bones. Other frequently involved site was local lymph nodes. The majority of these metastases were associated with local recurrences (n = 21/53; 40%). Median overall survival from diagnosis was 84 months (95% CI: 46–122). Median overall survival after the detection of metastases was 44 months (95% CI: 11–76, Figure 1).

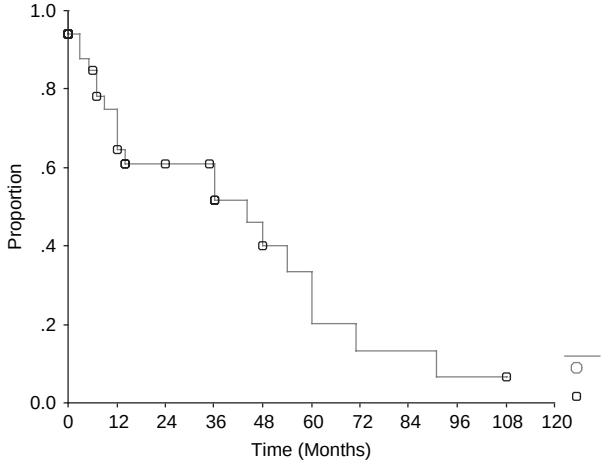

Figure 1. Overall survival of metastatic granular cell tumor patients after metastases.

It may be concluded that patients who have undergone surgical resection for GCT should be followed up closely at least during the first 2 years, especially if unfavorable histological features are present. In case metastases develop, surgical resection should be attempted whenever feasible, because neither radiotherapy nor chemotherapy appear particularly effective. Chemotherapy has been given to several cases, but no effective agent has emerged, and currently chemotherapy should be reserved only for very selected patients.

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