

## Diagnosis of a previously unidentified primary site in patients with spinal metastasis: diagnostic usefulness of laboratory analysis, CT scanning and CT-guided biopsy

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**Abstract** When the primary site is unknown in patients with spinal metastases, there can be problems in locating the site of tumor origin. Most previous reports on metastases of unknown origin have not been limited to the spine. The purpose of this study is to assess the usefulness of laboratory analysis, chest, abdominal and pelvic CT and CT-guided biopsy in patients with spinal metastases of unknown origin (SMUO). A retrospective review of the clinical histories of 27 patients with SMUO was done. A total of 43 patients with SMUO were seen at our institution between 2002 and 2007. Of the 43 patients, 27 who underwent all 3 tests (laboratory analysis including M protein and tumor markers, chest, abdominal and pelvic CT and CT-guided biopsy) were included in this study. We retrospectively assessed the diagnostic usefulness of those 3 tests in the 27 patients. In 27 patients, the final diagnosis was obtained in 26 patients. Myeloma was the most common malignancy followed by lung carcinoma. M protein was positive in all 7 patients with myeloma and negative in patients with other malignancies. The level of tumor markers was elevated in 16 of 17 patients with a solid tumor and in all 3 with lymphoma. CA15-3 was elevated in 4 of 27 patients, CA19-9 in 5 of 27 patients, CA125 in 2 of 27 patients, CEA in 6 of 27 patients, SCC in 2 of 27 patients, NSE in 7 of 27 patients, AFP in 1 of 27 patients, PIVKA-II in 1 of 27 patients, TPA in 6 of 27 patients, IAP in 3 of 12 patients, thyroglobulin in 2 of 27 patients, sIL-2R

in 3 of 24 patients, and PSA in 5 of 17 male patients. Myeloma, lymphoma and prostate carcinoma had a marker with high sensitivity and specificity (M protein, sIL-2R and PSA). Eleven primary tumor sites (40.7%) were detected (6 lung, 1 prostate, 1 kidney, 1 thyroid, 1 liver, and 1 pancreas) by chest, abdominal and CT scanning. Biopsy led to determination of the final diagnosis in 12 (44.4%) of 27 patients (5 myelomas, 3 lymphomas, 2 prostate carcinomas, 1 renal-cell carcinoma, 1 thyroid carcinoma). In the remaining 15 patients, biopsy did not lead to determination of the final diagnosis, because the histological diagnosis was either an adenocarcinoma or an undifferentiated carcinoma, the tissue sample was not diagnostic. A laboratory analysis limited to specific tumor markers such as PSA and protein electrophoresis is considered to be useful in making a final diagnosis. Chest, abdominal and pelvic CT is considered to be useful for making a final diagnosis in solid tumors, but not for hematologic tumors. A CT-guided biopsy had a low determination rate in the final diagnosis in comparison to a laboratory analysis and CT scanning for solid tumors and it is not considered to be essential for the diagnosis of hematologic tumors.

**Keywords** Spinal metastases of unknown origin · Diagnosis

### Introduction

The skeleton is a common metastatic site for visceral tumors. A metastatic tumor involves the spine more often than any other segment of the bony skeleton. Since most metastases occur after the detection of the primary tumor, the clinical diagnosis of a metastatic tumor of a spinal lesion can often be made from the patients' history. When

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the primary site is unknown, however, there are problems in locating the site of tumor origin. Although several articles on metastases of unknown origin have been reported, most of these studies have not been limited to the spine. The purpose of the current study was to assess the diagnostic usefulness of laboratory analysis, chest, abdominal and pelvic CT and CT-guided biopsy in patients with spinal metastases of unknown origin (SMUO).

## Materials and methods

A retrospective review was carried out of 43 consecutive patients with SMUO, who had no history of malignant disease at the time of presentation, treated between 2002 and 2007. This review included patients with hematologic tumors (myeloma and lymphoma), because the therapeutic issues associated with this generally widely metastatic malignancy resemble those of other spinal metastases [13]. Of the 43 patients, 27 fulfilled the following criteria for inclusion in the study. First, a laboratory analysis of blood sample including M protein (protein electrophoresis) and all following markers was performed. The tumor markers consisted of carcinoembryonic antigen (CEA), carbohydrate antigen 15-3 (CA15-3), carbohydrate antigen 19-9 (CA19-9), cancer antigen 125 (CA125), squamous cell carcinoma related antigen (SCC), neuron-specific enolase (NSE),  $\alpha$ -fetoprotein (AFP), protein induced by vitamin K absence antagonist-II (PIVKA-II), tissue polypeptide antigen (TPA), immunosuppressive acidic protein (IAP), thyroglobulin and sIL-2R (soluble interleukin-2 receptor). Furthermore, prostate specific antigen (PSA) was added in male patients. (the cutoff values of the markers were as follows: CEA 2.5 ng/ml; CA15-3, 25 U/ml; CA19-9, 37 U/ml; CA125, 35 U/ml; SCC, 1.5 ng/ml; NSE, 10.0 ng/ml; AFP, 10.0 ng/ml, PIVKA-II, 40 m AU/ml; TPA, 70 U/l; IAP, 604  $\mu$ g/ml; thyroglobulin, 30.0 ng/ml; sIL-2R, 483 U/ml; and PSA, 4.0 ng/ml.) Second, computed tomography (CT) scanning of the chest, abdomen and pelvis was performed to search for the primary visceral tumors. Finally, a CT-guided biopsy of the spinal lesion was performed to determine the histological diagnosis.

## Results

The patients' characteristics are shown in Table 1. They included 17 men and 10 women with an average age of 62.5 years (range, 30–78 years). Among these 27 patients, the final diagnosis was finally obtained in 26 patients. Myeloma was the most common malignancy followed by lung carcinoma, prostate carcinoma and lymphoma. M

protein in serum protein electrophoresis was positive in all 7 patients with myeloma and negative in patients with other malignancies. The level of tumor markers was elevated in 16 of 17 patients with a solid tumor and all 3 with lymphoma. CA15-3 was elevated in 4 of 27 patients, CA19-9 in 5 of 27 patients, CA125 in 2 of 27 patients, CEA in 6 of 27 patients, SCC in 2 of 27 patients, NSE in 7 of 27 patients, AFP in 1 of 27 patients, PIVKA-II in 1 of 27 patients, TPA in 6 of 27 patients, IAP in 3 of 27 patients, thyroglobulin in 2 of 27 patients, sIL-2R in 3 of 24 patients and PSA in 5 of 17 male patients. The sensitivities, specificities, and positive predictive values of M protein and each tumor marker for four main tumors are shown in Table 2. Of those tumors, myeloma, lymphoma and prostate carcinoma had a marker with high sensitivity and specificity (M protein, sIL-2R and PSA). However, no marker with adequate sensitivity was found in lung carcinoma.

Determination rate of final diagnosis in chest, abdominal and pelvic CT and CT-guided biopsy were shown in Table 3. CT of the chest, abdomen and pelvis demonstrated 11 primary tumor sites (40.7%): six patients had carcinoma of the lung; one, the prostate; one, the kidney; one, the thyroid; one, the liver; and one, the pancreas.

Twenty-two (81.5%) of 27 patients had a malignancy histologically confirmed by biopsy of the spinal lesion. The histological diagnoses were eight adenocarcinomas, five myelomas, two prostate carcinomas, three lymphomas, two undifferentiated carcinomas, one each of renal-cell carcinoma, well differentiated thyroid carcinoma. The biopsy findings led to a final diagnosis in 12 (44.4%) of 27 patients: one who had five myelomas, three lymphomas, two prostate carcinomas, one each of renal-cell carcinoma and thyroid carcinoma. In the remaining 15 patients, the biopsy did not lead to determination of the final diagnosis, because the histological diagnosis was either an adenocarcinoma or an undifferentiated carcinoma, or the tissue sample was not diagnostic.

## Discussion

About 10% of all cancer patients develop metastases to the spine [3, 5, 6]. Among adults, 60% of spinal metastases are either from breast, lung, or prostate carcinoma. Renal and gastrointestinal malignancies each account for about 5% of spinal metastases, while thyroid carcinomas comprise a lower percentage [1, 2, 4]. In the present series, lung carcinoma was the most common solid tumor followed by prostate carcinoma and there was no case of breast carcinoma. It has been speculated that spinal metastasis is usually found after a diagnosis of breast carcinoma since it has a prolonged prognosis.

**Table 1** Patient characteristics

Patient no.	Sex	Age (years)	Presenting spinal site	Laboratory analysis	Chest, abdominal and pelvic CT	CT-guided biopsy (histological diagnosis)	Final diagnosis
1	M	59	T	M protein	Bone lesion only	Not diagnostic	Myeloma
2	M	59	L	M protein, PSA	Bone lesion only	Myeloma	Myeloma
3	M	35	T	M protein	Bone lesion only	Myeloma	Myeloma
4	M	76	T	M protein	Bone lesion only	Myeloma	Myeloma
5	F	30	L	M protein	Bone lesion only	Not diagnostic	Myeloma
6	F	70	T	M protein	Bone lesion only	Myeloma	Myeloma
7	M	58	L	M protein	Bone lesion only	Myeloma	Myeloma
8	F	48	T	sIL-2R, NSE	Bone lesion only	Lymphoma	Lymphoma
9	F	78	L	sIL-2R, IAP	Bone lesion only	Lymphoma	Lymphoma
10	M	65	T	sIL-2R	Bone lesion only	Lymphoma	Lymphoma
11	F	66	L	CA19-9, CA125, CEA, SCC	Lung mass	Adenocarcinoma	Lung carcinoma
12	F	59	L	CA125, CEA, NSE, TPA	Lung mass	Adenocarcinoma	Lung carcinoma
13	M	56	T, L	CEA, CA19-9	Lung mass	Adenocarcinoma	Lung carcinoma
14	F	69	T	SCC	Lung mass	Adenocarcinoma	Lung carcinoma
15	M	55	T	Thyroglobulin, NSE	Lung mass	Adenocarcinoma	Lung carcinoma
16	M	69	C	PSA	Lung mass	Adenocarcinoma	Lung carcinoma
17	M	70	T	PSA, CA15-3, IAP	Prostate mass	Prostate carcinoma	Prostate carcinoma
18	M	56	T	PSA, CA19-9, CEA, TPA, NSE,	Bone lesion only	Undifferentiated carcinoma	Prostate carcinoma
19	M	77	T, L	PSA	Bone lesion only	Prostate carcinoma	Prostate carcinoma
20	M	72	T	PSA, CA15-3, NSE	Bone lesion only	Not diagnostic	Prostate carcinoma
21	M	71	T	CA15-3, IAP	Kidney mass	Renal-cell carcinoma	RCC
22	F	72	T	Thyroglobulin, CA19-9	Thyroid mass	Well differentiated carcinoma	Thyroid carcinoma
23	M	64	T	AFP, PIVKA-II, NSE, TPA	Liver mass	Not diagnostic	HCC
24	F	54	C	CA15-3, CA19-9, CEA, NSE, TPA	Pancreas mass	Undifferentiated carcinoma	Pancreas carcinoma
25	F	66	T, L	CEA, TPA	Bone lesion only	Adenocarcinoma	Stomach carcinoma
26	M	77	T	Within normal limits	Bone lesion only	Not diagnostic	Esophagus carcinoma
27	M	57	T	TPA	Bone lesion only	Adenocarcinoma	Uncertain

*L* lumbar, *T* thoracic, *C* cervical, *RCC* renal-cell carcinoma, *HCC* hepatocellular carcinoma

It has been reported that a spinal malignancy of unknown origin is often derived not only from solid tumors, but also from hematologic tumors [13]. In this series, myeloma was the most common etiology of SMUO and serologic evaluation for monoclonal gammopathy was very useful in all seven patients with myeloma. Therefore, serum protein electrophoresis should be performed as an initial routine study.

Increased serum levels of sIL-2R have been reported in various hematologic tumors including lymphoma [9, 10, 12]. The serum sIL-2R had high sensitivity and specificity in patients with lymphoma in this series; therefore, sIL-2R was considered useful for the diagnosis of lymphoma in patients with SMUO.

Tumor markers were abnormally elevated in all but one patient with solid tumors in the current study.

Although most markers lack adequate specificity to identify the primary lesion, abnormal elevation of serum PSA, AFP and/or PIVKA-II and thyroglobulin have been reported to be considerably specific to prostate, liver and thyroid, respectively [7, 8, 14–17]. In this study, prostate carcinoma was common etiology of SMUO and PSA had high sensitivity and specificity in patients with prostate carcinoma. Furthermore, AFP/PIVKA-II and thyroglobulin were elevated in hepatocellular and thyroid carcinoma, respectively. From the results of the current study, examinations of tumor makers limited to specific tumor markers such as PSA, AFP, PIVKA-II and thyroglobulin is considered to be useful for identifying the site of primary solid tumors.

In the present series, a CT-guided biopsy led to the determination of the final diagnosis in 44.4% patients,

**Table 2** Sensitivities, specificities, and positive predictive values of M protein and tumor marker for four different tumor

	Myeloma			Lymphoma			Lung			Prostate		
	Sensitivity (%)	Specificity (%)	PPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)
M protein	100	100	100	0	69.5	0	0	66.6	0	0	69.5	0
CEA	0	70	0	0	73.9	0	50	85.7	50	25	78.2	16.6
CA15-3	0	80	0	0	82.6	0	0	80.9	0	50	91.3	50
CA19-9	0	75	0	0	78.2	0	33.3	85.7	40	25	82.6	20
CA125	0	90	0	0	91.3	0	33.3	100	100	0	91.3	0
SCC	0	85	0	25	95.6	50	33.3	95.2	66.6	0	86.9	0
NSE	0	65	0	25	73.9	14.2	33.3	76.1	28.5	50	78.2	28.5
AFP	0	95	0	0	95.6	0	0	95.2	0	0	95.6	0
PIVKA-II	0	95	0	0	95.6	0	0	95.2	0	0	95.6	0
TPA	0	70	0	0	73.9	0	16.7	76.1	16.6	25	78.2	16.6
IAP	0	85	0	25	91.3	33.3	0	85.7	0	25	91.3	33.3
Thyroglobulin	0	85	0	25	91.3	33.3	16.7	90.4	33.3	0	91.3	0
sIL-2R	0	85	0	100	100	100	0	85.7	0	0	86.9	0
PSA	14.3	75	16.6	0	73.9	0	16.7	76.1	16.6	100	91.3	66.6

PPV positive predictive value

**Table 3** Determination rate of final diagnosis

	Total [% (no.)]	Hematologic tumor [% (no.)]	Solid tumor [% (no.)]
Chest, abdominal and pelvic CT	40.7 (11/27)	0 (0/10)	64.7 (11/17)
CT-guided biopsy	44.4 (12/27)	80.0 (8/10)	23.5 (4/17)

especially, in 80.0% of patients with hematologic tumors. However, similar to the findings of previous reports [5, 11], it is not logical to start the search with a needle biopsy in patients with SMUO from the following reasons. First, a biopsy requires an invasive procedure. Second, it is not essential for making a final diagnosis in patients with hematologic tumors, although it does have a high determination rate for the final diagnosis. Third, the determination rate of the final diagnosis in solid tumors is low in comparison to a laboratory analysis and CT scanning.

In conclusion, a laboratory analysis limited to specific tumor markers such as PSA and protein electrophoresis is therefore considered to be useful in making a final diagnosis in such patients. Chest, abdominal and pelvic CT is considered to be useful for making a final diagnosis in solid tumors, but not for hematologic tumors. A CT-guided biopsy had a low determination rate in the final diagnosis in comparison to a laboratory analysis and CT scanning for solid tumors and it is therefore not considered to be essential for the diagnosis of hematologic tumors because a laboratory analysis was found to be an alternative.

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