The Incidence of Nonmalignant Diseases among Patients with Suspected Carcinoma of Unknown Primary Site

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Abstract:

Objective Few reports have analyzed the diagnostic process of carcinoma of unknown primary site (CUP) or have focused on the frequency of nonmalignant lesions among patients with suspected malignant diseases. The aim of this study was to investigate the incidence and characteristics of nonmalignant diseases that tend to be mistaken for malignant diseases.

Patients We retrospectively analyzed the medical records of patients with suspected CUP who were referred to the National Cancer Center Hospital (Tokyo, Japan) between April 2007 and December 2014. All patients underwent a thorough history and physical examination as well as radiological and ultrasonography imaging tests for the CUP diagnostic work up.

Results Among 830 patients with suspected CUP, 46 were diagnosed with nonmalignant diseases, and 780 were diagnosed with a malignant neoplasm (409 neoplasms with detected primary site and 371 CUP neoplasms). Four patients discontinued the diagnostic workup because they refused further examinations or had a poor general status. The final diagnosis of the 46 patients with nonmalignant disease comprised 10 benign tumors, 10 benign diseases, and 26 with no evidence of disease. The nonmalignant tumors comprised three hemangiomas, two schwannomas, two uterine myomas, two pseudomyxoma peritonei, one lymphangioma, one meningioma, and one poroma.

Conclusions The incidence of nonmalignant diseases among patients with suspected CUP was 46 out of 830 patients in our institution. It is important to perform a thorough pathological examination in the CUP diagnostic workup. To confirm a diagnosis, some patients may need to visit specialized institutions, especially those with liver and bone lesions.

Key words: carcinoma, diagnosis, incidence, nonmalignant disease, tuberculosis, biopsy

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Introduction

Carcinoma of unknown primary site (CUP) is pathologically a metastatic carcinoma for which conventional diagnostic work up fails to detect the primary site (1). CUP represents a heterogeneous group of malignant diseases and accounts for approximately 2%-10% of all solid malignant tumors (2, 3). Metastatic disease of unknown primary origin (MUO) is the status of patients suspected of having malignant disease for which the primary site is not detected in limited clinical examinations or by imaging modalities, based on the guidelines of the National Institute for Health and Clinical Excellence (NICE) (4).

The final diagnosis of MUO with a systematic diagnostic work-up includes benign diseases, nonmalignant tumors,
malignant tumors with detected primary sites and confirmed CUP. Confirmed CUP is defined as metastatic epithelial or neuro-endocrine malignancy identified on the basis of the final histopathological findings. If the primary site is not detected then performing selected initial screening, a specialized review, and further specialized investigations are recommended according to the NICE guidelines (4).

Determining the primary site heavily influences modern cancer management. Patients with CUP have worse survival outcomes than patients with other advanced cancer or patients with a detected primary site who are suspected of having CUP (5-7). Patients with CUP were divided into two groups after a comprehensive work-up to detect the primary site: “favorable” and “unfavorable” subsets. According to our previous report, among patients in the unfavorable subset with a poor prognosis, those defined as having CUP with a putative primary breast or ovarian cancer according to clinicopathological features had a better prognosis than the others (8). An immediate work-up with the aim of detecting the primary site is therefore essential for all patients with suspected CUP.

The standard diagnostic workup for CUP in recent guidelines includes a careful physical examination, computed tomography (CT), and histopathological analysis with a biopsy or surgical resection to confirm malignancy and to gain additional information regarding the primary site (4, 32). Although there is some evidence of the advantages of focused imaging and gene expression analyses (9, 10), a nonmalignant lesion cannot be excluded with a single imaging modality to diagnose CUP. The importance of determining a primary site has long been demonstrated; however, few reports have analyzed the diagnostic process of CUP. Furthermore, no report exists concerning the frequency of nonmalignant lesions among patients suspected of having MUO and referred to specialized facilities.

This study aimed to investigate the frequency of nonmalignant disease in patients with MUO in a tertiary hospital and the clinical features of disorders that tend to be mistaken for malignant lesions.

Materials and Methods

We retrospectively investigated the medical records of patients suspected of having CUP or MUO and referred to the National Cancer Center Hospital (Tokyo, Japan) between April 2007 and December 2014. Our hospital is a specialized cancer hospital in Japan, and many patients suspected of having cancer or MUO are referred to this institution. We systematically perform clinical examinations and tests on all patients suspected of having MUO at our institution, according to the clinical guidelines. The following patients were included in this study: patients who had previously undergone a biopsy at another hospital, those who did not undergo a biopsy before being referred to our hospital. In addition, all of the patients suspected of having CUP at our institution were required to undergo the following procedures based on the guidelines: a thorough history-taking and physical examination; radiological and ultrasonography imaging tests [including X-ray imaging, CT, magnetic resonance imaging (MRI), and positron emission tomography (PET)]; and referral to specialized departments for the determination of a histopathological diagnosis, which included a review of the prior diagnosis, if necessary. We excluded from further analysis any patients who met the following criteria: (1) patients with a clinical diagnosis with histological proof of malignancy (confirmed CUP), and (2) patients who refused medical care.

The precise data of the patients diagnosed with nonmalignant diseases were collected from clinical records. We investigated each patient’s age, sex, performance status (PS), based on the Eastern Cooperative Oncology Group criteria, medical history of malignant neoplasm, pathology, response to the referral to a specialist, results and expert reports of the imaging tests, final diagnosis by a clinician, and the basis for the final diagnosis. The data of the clinical course after the patient’s last visit to our hospital were collected from the medical records and letters from other hospitals.

This study was approved by the institutional review board of the National Cancer Center Hospital (approval number, 2012-335). Individual patient approval was not requested by the board.

Results

Among the 830 patients with suspected CUP who were referred to our hospital during the period, 780 (94.0%) were diagnosed with a malignant neoplasm (409 patients in whom the primary site was detected, and 371 patients with CUP), and 46 (5.5%) patients were diagnosed with nonmalignant diseases. Four (0.5%) patients discontinued the diagnostic workup because they refused further examinations or had a poor general status. The diagnostic flow chart is shown in Figure. The median age, sex, PS, disease distribution, and reasons for referral to our oncology center are listed in Tables 1 and 2.

Among the 46 patients diagnosed with nonmalignant diseases, we determined a distinct diagnosis in the 35 (76%) who had undergone a diagnostic work-up and specialists’ consultation (e.g. gynecologists and/or urologists) at our institution. Eight patients were diagnosed with nonmalignant diseases, based on the clinical course and previous test results. The other three patients were examined and diagnosed with nonmalignant diseases (e.g. rheumatoid arthritis, sarcoidosis, and tuberculous lymphadenopathy) at other institutions.

Table 2 shows the 35 patients who had a distinct diagnosis after the diagnostic workup. Twenty-one patients examined at our institution were diagnosed by pathological tests (18 biopsies and 3 expert reviews). After conducting an additional review of the imaging tests at our institution, a diagnosis was determined for 10 patients. The remaining four patients were diagnosed following a specialist consultation.
Patients suspected CUP n=830

Patients refusal n=4

Malignancy n=780

CUP n=409

Non malignancy n=46

Detected primary site n=371

Additional tests and experts reports In our institution n=35

Clinical course and previous test results In our institution n=8

Diagnosed in other institutions n=3

Figure. The CONSORT diagram. CONSORT: Consolidated Standards of Reporting Trials, CUP: carcinoma of unknown primary site

| Table 1. Patients’ Characteristics. | No. of patients (n=46) |
|-----------------------------------|-----------------------|
| Age, year, median (range)         | 65 (19-80)            |
| Sex                               |                       |
| Male                              | 19 (41%)              |
| Female                            | 27 (59%)              |
| PS                                |                       |
| 0                                 | 30 (65%)              |
| 1                                 | 11 (24%)              |
| ≥2                                | 1 (2%)                |
| NA                                | 4 (9%)                |
| History of malignancy             |                       |
| None                              | 42 (92%)              |
| Gastric cancer                    | 1 (2%)                |
| Breast cancer                     | 2 (4%)                |
| Bladder cancer                    | 1 (2%)                |

PS: European Cooperative Oncology Group Performance Status, NA: not available
The data are presented as the no. (%), unless otherwise indicated.

Table 2. Reasons of MUO for Referral to Our Institution.

| Reason                                      | No. of patients (n=46) |
|---------------------------------------------|-----------------------|
| Bone lesion                                 | 11 (24%)              |
| Lung/mediastinum lesion                     | 7 (15%)               |
| Increased tumor marker level                | 7 (15%)               |
| Ascites                                     | 6 (13%)               |
| Abdominal mass (excluding LM)               | 6 (13%)               |
| Lymphadenopathy                             | 3 (7%)                |
| Liver mass                                  | 3 (7%)                |
| Mammary/thyroid mass                        | 1 (2%)                |
| Subcutaneous mass                           | 1 (2%)                |
| Ureteral stenosis                           | 1 (2%)                |

MUO: metastatic disease of unknown primary origin, LM: liver mass
The data are presented as the no. (%).

Discussion

To our knowledge, this is the first study to show the prevalence and differential diagnosis of nonmalignant disease among patients with suspected CUP in a tertiary referral hospital. In this study, 46 (5.5%) of 830 patients with suspected CUP who were referred to our hospital were ultimately diagnosed with nonmalignant diseases, either pathologically or clinically. In our study, 35 of 46 patients were diagnosed with nonmalignant diseases at our hospital; the remaining 3 patients were subsequently diagnosed at other hospitals. Of the 35 nonmalignant diagnoses, 21 were diagnosed based on pathological examinations (18 via additional biopsies and 3 via pathological reviews of the prior histopathological specimen), while the remainder were diag-
undergoing the histopathological diagnostic procedure of malignancy; however, some patients have difficulty undergoing the histopathological diagnostic procedure and an expert review (4 patients).

Table 3. The Distinct Diagnoses and Additional Diagnostic Procedures Performed at Our Institution.

| Basis                                           | No. (n=46) | The reason of additional diagnostic procedure                                                                 | Diagnosis                                                                 |
|-------------------------------------------------|------------|-------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Additional biopsy*                              | 18 (52%)   | No biopsy at prior hospital                                                                                  | Benign tumor (hemangioma, schwannomas, uterine myomas) (n=3)               |
| Bone lesion                                     | 7 (20%)    | No biopsy at prior hospital                                                                                  | No evidence of malignancy (n=3)                                            |
|                                                 |            |                                                                                                             | Tuberculosis (n=1)                                                        |
| Lung/mediastinum lesion                         | 5 (14%)    | No biopsy at prior hospital                                                                                  | No evidence of malignancy (n=2)                                            |
|                                                 |            |                                                                                                             | Benign tumor (schwannomas, uterine myomas) (n=2)                           |
|                                                 |            |                                                                                                             | Tuberculosis (n=1)                                                        |
| Abdominal mass                                  | 2 (6%)     | Insufficient specimen at prior hospital                                                                     | Benign tumor (lymphangioma) (n=1)                                         |
| Liver mass                                      | 2 (6%)     | Insufficient specimen at prior hospital                                                                     | Tuberculosis (n=1)                                                        |
| Lymph node                                      | 1 (3%)     | No biopsy at prior hospital                                                                                  | Benign tumor (neurofibromatosis) (n=1)                                    |
| Mammary/thyroid mass                            | 1 (3%)     | No biopsy at prior hospital                                                                                  | No evidence of malignancy (n=1)                                            |
| Additional or review of imaging tests**         | 10 (28%)   | No biopsy at prior hospital                                                                                  | No evidence of malignancy (n=6)                                            |
| Tumor marker increased                          | 2 (6%)     | No imaging recommended by guidelines at prior hospital.                                                     | No evidence of malignancy (n=6)                                            |
| Lung lesion                                     | 1 (3%)     | No biopsy at prior hospital                                                                                  | No evidence of malignancy (n=6)                                            |
| Ascites                                         | 2 (6%)     | Insufficient specimen at prior hospital                                                                    | No evidence of malignancy (n=6)                                            |
| Bone                                            | 1 (3%)     | Insufficient specimen at prior hospital                                                                    | No evidence of malignancy (n=6)                                            |
| Intraabdominal lesion                           | 3 (8%)     | At prior hospital, no imaging which is recommended by guidelines. So the patients needed additional biopsy  | No evidence of malignancy (n=1)                                            |
|                                                 |            |                                                                                                             | contrast CT imaging and radiology expert review                            |
|                                                 |            |                                                                                                             | Suspected hemangioma and additional MRI scan was needed                   |
|                                                 |            |                                                                                                             | Benign tumor (peritoneal hemangioma)                                     |
|                                                 |            |                                                                                                             | (n=2)                                                                     |
| Uterine lesion                                  | 1 (3%)     | Additional MRI scan was needed for qualitative diagnosis                                                    | Infection with uterine myoma (n=1)                                        |
| Additional expert review***                     | 4 (11%)    | Specialized gynecological examination were needed because of female gender with ascites                    | No evidence of malignancy (n=1)                                            |
| Ascites                                         | 2 (6%)     | Specialized gynecological examination were needed because of female gender with ascites                    | Cirrhosis (n=1)                                                           |
| Tumor marker increased                          | 1 (3%)     | Specialized gynecological examination were needed because of female gender with CA125 increased          | No evidence of malignancy (n=1)                                            |
| Ureteral stenosis                               | 1 (3%)     | Urological examination was needed because of suspicion of ureteral stenosis by imaging test                | No evidence of malignancy (n=1)                                            |
| Review of pathology                             | 3 (9%)     |                                                                                                             | No evidence of malignancy (n=1)                                            |
| Bone lesion                                     | 1 (3%)     | All histopathology must be reviewed in our hospital                                                        | Benign tumor (meningioma) (n=1)                                           |
| Subcutaneous mass                               | 1 (3%)     |                                                                                                             | Benign tumor (poroma) (n=1)                                               |
| Liver mass                                      | 1 (3%)     |                                                                                                             | No evidence of malignancy (n=1)                                            |

The data are presented as the no. (%).

*Among the patients with 1 liver mass (fatty liver) and 1 abdominal mass (lymphangioma), significant specimen for definitive diagnosis could not be obtained in the institutions that referred to our hospital. Among the other patients, biopsy was not performed.

**Definitive diagnosis was confirmed by additional or review of MRI in 5, and PET-CT in 2.

***2 patients who were referred to our institution because of ascites (1 no evidence of malignancy and 1 cirrhosis) and 1 patients referred for tumor marker increased (no evidence of malignannacy) in gynecology department. The patient who was referred for ureteral stenosis was diagnosed in urology department.

Tumor marker increased (10 patients) based on a review of imaging test results (10 patients) and an expert review (4 patients).

The definition of CUP requires the pathological confirmation of malignancy; however, some patients have difficulty undergoing the histopathological diagnostic procedures (2, 3). In a previous report (11), among 1,285 patients diagnosed with CUP in the Netherlands, 261 (20%) were diagnosed clinically without any histopathological examinations. Furthermore, among MUO patients, not all lesions are malignant. One case series (12) conducted at a cancer center...
in the United Kingdom performed bone biopsies of suspected malignant lesions from patients who had a history of cancer. In that report, 3 (10%) of 30 lesions were reported as benign.

Advances in imaging techniques have aided in the detection of primary lesion before invasive interventions. Positron emission tomography-computed tomography (PET-CT) is especially indicated for patients with squamous cell cervical lymphadenopathy or solitary metastases of CUP (13-17). The diagnostic value of PET-CT for cervical CUP includes a sensitivity of 87% and specificity of 88% (18). Previous reports have indicated a malignancy rate of 89.2% for questionable lesions identified by PET-CT that underwent a biopsy examination (19). However, the false-positive results with PET-CT range from 5% to 18%, and pathological examinations reveal findings such as benign tumors, inflammation, and normal tissue in the thyroid (20-22). In addition, among patients with primary carcinoma, the malignancy rate of bone lesions that underwent a biopsy was 79%-98% (23, 24). For liver lesions, the malignancy rate of liver masses that were detected radiologically and underwent a biopsy was 88.1% (25). For this reason, we cannot confirm CUP without a histopathological assessment in cases where a biopsy of the lesion is difficult. In addition, the present study showed that thorough imaging tests, including MRI, might be significant in patients with single lesions deep in the body or hypervascular lesions that are difficult to biopsy (Table 3).

With regard to the diagnostic management of CUP, determining the site of a metastatic lesion is important for predicting a patient’s prognosis. Several reports have indicated the following to be prognostic factors of CUP: male sex, poor PS, high number of metastatic sites, presence of liver metastases, and elevated alkaline phosphatase levels (26-29). Previous studies have indicated that bone and liver lesions are the most powerful independent adverse prognostic factors (30, 31). Among patients who were diagnosed by additional pathological procedures at our institution, 50% (9/18) had bone or liver lesions. In our study, 18 patients underwent an additional biopsy at our institution. Most (16/18) particularly those with bone, lung, mediastinal and liver lesions, had not undergone a biopsy at prior institutions. These sites are sometimes difficult to biopsy at community hospitals, suggesting the importance of referring patients with mass lesions at these sites to specialized institutions for a definitive diagnosis.

We performed additional surgical procedures and confirmed the diagnosis in four patients with tuberculosis lesions. None of these patients had ever undergone a biopsy or surgical resection for an evaluation prior to being referred to our institution. Tuberculosis is an important public health disease that mimics malignant lesions. In addition, CUP with bone and/or liver lesions is associated with a poor prognosis. Therefore, in difficult cases, it is important to refer patients with a bone or liver mass to specialized institutions and consider a biopsy of these lesions.

The present study has several limitations. First, the sample size was small, which may have contributed to the low frequency of CUP. The importance of determining a diagnosis based on pathological results is widely recognized in the modern clinical setting. However, it is worth noting that patients with nonmalignant diseases such as tuberculosis need to visit specialized institutions. More clinical cases are required to establish the precise indication for a referral. Second, it is difficult to prove the nonexistence of a disease. However, no patient was referred again to our institution or was subsequently diagnosed with malignant tumors. After we referred the patients for further examinations, the diagnostic rate of nonmalignant diseases (e.g. rheumatoid arthritis, sarcoidosis, and tuberculous lymphadenopathy) that were confirmed at other institutions was 6.5% (3/46 patients).

Conclusion
In conclusion, we demonstrated the importance of performing a thorough pathological examination and showed that some patients-especially those with liver and bone lesions-need to be referred to specialized institutions for the confirmation of a malignant or nonmalignant tumor. We would also like to highlight the importance of excluding tuberculosis.

Author’s disclosure of potential Conflicts of Interest (COI).
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