Metachronous double primary cancer of epithelial and mesenchymal origins
A case report of a rare clinical phenomenon

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Abstract

Rationale: Metachronous double primary cancers from the same origin have previously been reported in several studies; however, the occurrence of double primary cancers from different tissue origins has not been reported earlier.

Patient concerns: We analyzed 10 patients with requirement surgical treatment.

Diagnoses: After over 6 months of the surgery, histopathological examination confirmed the presence of at least two neoplastic lesions with distinct histopathology at different locations.

Interventions: These patients underwent surgery and the hematoxylin and eosin staining was performed according to standard protocol in all cases.

Outcomes: Since the occurrence of multiple primary cancers is an extremely rare event, it is difficult to find a large sample size of patients with double primary cancers at one study center. All patients included in this study received surgical therapy twice and had a final tissue histopathologic diagnosis.

Lessons: Based on our findings, it is concluded that a prolonged follow-up examination for cancer patients should be taken into consideration to provide early detection of secondary tumors and improve overall life expectancy of these patients. Furthermore, clinicians should be well aware of the possibility of cancer patients developing a second primary cancer of a different tissue origin.

Abbreviations: HE = hematoxylin and eosin, EMT = epithelial-mesenchymal transition.

Keywords: cancer, double primary malignancy, metachronous

1. Introduction

According to American Association for Cancer Research, cancer cases worldwide are expected to increase from 15.2 million, as reported in 2015, to 24 million in 2035.1 At the same time, advances in treatment have increased the number of cancer survivors, and many new cases of metachronous double primary cancers of different tissue origins have been reported. In 1934, double primary malignancies were first reported by Bugher,2 who analyzed its statistical features. However, double primary malignancies of epithelial or mesenchymal origin have not been reported to date. To our knowledge, this is the first study reporting 10 cases of double primary malignancies of either epithelial or mesenchymal origin. Additionally, we present the clinical and pathological characteristics of these malignancies, as observed in patients participating in this study. These cases presented epithelial and mesenchymal tumors at the primary and secondary sites, respectively; however, the molecular pathway mediating this phenomenon remains to be determined. This study aims to better inform the clinical oncologists of the rising incidence of metachronous primary malignancies in cancer survivors.

2. Patient information

In this retrospective study, we analyzed 10 patients with various types of malignancies, and none of them were observed to have metastasis at the time of the first surgery. These patients underwent surgery at our Cancer Center between January 1995 and December 2015. In all cases, hematoxylin and eosin (HE) staining was performed according to standard protocol. All specimens were critically reviewed to confirm the pathological features and no patient showed symptoms of any other malignancies. The inclusion criteria of patients enrolled in this study were as follows: (1) metachronous malignancies were defined as secondary tumors that developed ≥6 months after the first malignancy; (2) histopathological examination confirmed the presence of at least 2 neoplastic lesions with distinct histopathology at different locations; (3) the presence of at least 2 cm of normal mucosa between the tumors, and if the tumors were observed in the same location, then their occurrence had to be at least 5 years apart; (4) probability of the second tumor resulting from metastasis of the first tumor was excluded. Patients who did not meet the inclusion criteria were excluded from our study. Furthermore, all patients with the
Table 1. Clinicopathological variables of the 10 patients.

| No. | Sex | Age, years | Primary site     | Histopathology      | Second site         | Histopathology         | Time interval, months |
|-----|-----|------------|------------------|---------------------|---------------------|------------------------|----------------------|
| 1   | F   | 66         | Left renal       | Clear cell carcinoma| Sacrococcygeal      | Synovial sarcoma       | 132                  |
| 2   | F   | 51         | Thyroid gland    | Papillary carcinoma | Left upper arm      | Clear cell carcinoma   | 72                   |
| 3   | M   | 64         | Gastric          | Adenocarcinoma      | Right groin         | Synovial sarcoma       | 9                    |
| 4   | F   | 58         | Rectum           | Adenocarcinoma      | Right thigh         | Polymorphic undifferentiated sarcoma | 8                  |
| 5   | F   | 71         | Right lung       | Squamous carcinoma  | Left thigh          | Polymorphic undifferentiated sarcoma | 60                 |
| 6   | F   | 59         | Rectum           | Adenocarcinoma      | Left leg            | Undifferentiated sarcoma | 13                 |
| 7   | M   | 76         | Oesophagus       | Squamous carcinoma  | Right chest wall    | Undifferentiated sarcoma | 240                |
| 8   | M   | 81         | Larynx           | Squamous carcinoma  | Right back          | Dermatofibrosarcoma protuberans | 17                 |
| 9   | F   | 45         | Right lung       | Adenocarcinoma      | Left thigh          | Alveolar sarcoma        | 9                    |
| 10  | F   | 65         | Left lung        | Squamous carcinoma  | Right axilla        | Fibrosarcoma            | 11                   |

Figure 1. The composition of primary (A) and second site malignancies (B).

Figure 2. Histopathologic examination of the excised tissues confirmed the pathology diagnosis (HE hematoxylin-eosin staining 100) (1 clear cell carcinoma—synovial sarcoma, 2 papillary carcinoma—clear cell carcinoma sarcomas, 3 adenocarcinoma—synovial sarcoma, 4 adenocarcinoma—polymorphic undifferentiated sarcoma, 5 squamous carcinoma—polymorphic undifferentiated sarcoma, 6 adenocarcinoma—undifferentiated sarcoma, 7 squamous carcinoma—undifferentiated sarcoma, 8 squamous carcinoma—dermatofibrosarcoma protuberans, 9 adenocarcinoma—alveolar sarcoma, 10 squamous carcinoma—fibrosarcoma). HE=hematoxylin and eosin.
following criteria were excluded from this study: (1) patients without a clear histopathological confirmation of each tumor, (2) patients who were suspected to develop the second tumor as a result of metastasis of the first location. This study complied with the Declaration of Helsinki and was approved by the Human Ethics and Research Ethics Committees of the Fourth Hospital of Hebei Medical University. All participating patients provided written informed consent.

3. Pathological findings

The summary of the clinical data for 10 patients (3 men and 7 women) is provided in Table 1. At the time of diagnosis of the primary cancer, the age of patients ranged from 45 to 81 years (mean age, 63.6 ± 10.9 years). The primary and secondary tumor sites are shown in Figure 1. The interval time, defined as the interval between the pathologic diagnosis of the first and second tumors, ranged from 8 months to 240 months (mean, 57.1 ± 76.0 months). All patients included in this study received surgical therapy twice and had a final tissue histopathologic diagnosis (Fig. 2).

4. Discussion

Over the years, there has been a significant increase in the number of cancer survivors. An overall rise in the median age of world population and advances in treatment has led to improved survival outcomes for cancer patients; however, these survivors live with high risks of subsequently developing a second primary tumor. Curtis et al studied a group of cancer patients in Connecticut and reported that these patients were at a 31% higher risk of developing a second primary cancer. In another study conducted by Kim and Song, metachronous double primary cancers were found in 108 out of 2657 breast cancer patients (4.1%), and the relative risk showed a significantly increased incidence of endometrial, stomach, and thyroid cancers. In our study, all 10 patients presented epithelial tumor at the primary and mesenchymal tumor at the secondary sites. These findings suggest that the epithelial–mesenchymal transition (EMT) pathway may play a key role in mediating cancer progression and metastasis.

Since the occurrence of multiple primary cancers is an extremely rare event, it is difficult to find a large sample size of patients with double primary cancers at one study center. Thus, a multicenter investigation should be undertaken in order to identify the predisposing factors associated with this malignancy, and to further develop more effective treatment strategies for the affected patients.

Acknowledgments

All authors have read and approved the final manuscript. The authors declare that they have no competing interests.

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