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Cisplatin plus Docetaxel Chemotherapy for Thoracic Lymph Node Metastasis from Cancer of Unknown Primary – Experience of Three Cases

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Key Words
Empiric chemotherapy · FDG-PET · Chemotherapy

Abstract
The optimal chemotherapeutic regimen for cancer of unknown primary (CUP) remains uncertain. We encountered 3 cases with CUP who presented with thoracic lymph node metastasis. Detailed physical examination and diagnostic tests, including laboratory investigations, bronchoscopy, upper and lower gastrointestinal studies, computed tomography of the head, neck, abdomen and pelvis and ^{18}F-fluorodeoxyglucose positron emission tomography, failed to identify the primary site in these cases. The patients were treated with the cisplatin plus docetaxel chemotherapy regimen. Concomitant thoracic radiotherapy was conducted in one patient and surgical resection in another. All patients showed good response to the chemotherapy and achieved long-term disease-free survival.

Introduction

Despite the development of excellent diagnostic tools, there still remain patients with metastatic cancer in whom the site of the primary tumor cannot be determined; these patients are defined as having cancer of unknown primary (CUP) [1, 2]. The prevalence

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of CUP reportedly accounts for approximately 2–5% of all cancer diagnoses [1, 2]. Although lymph nodes are the most common metastatic site of CUP [3], involvement of thoracic lymph nodes alone in cases of cancer of unknown primary site is quite rare [3–6]. We encountered 3 consecutive patients with CUP with metastases primarily involving the mediastinal lymph nodes during a 5-year period at our institute. All 3 patients were treated by combined cisplatin (CDDP) plus docetaxel (DOC) chemotherapy. All showed good responses to this chemotherapy, with prolonged disease-free survival. We describe our experience with these 3 cases along with a review of the relevant literature.

Case Presentation

Case 1

A 55-year-old man was referred to our hospital because of abnormal findings on chest computed tomography (CT) in October 2002. The patient had no history of smoking or any significant medical history. Physical examination revealed no abnormal findings except left supraclavicular lymph node swelling. Serum carcinoembryonic antigen (CEA) was elevated (11.6 ng/ml, normal <2.5 ng/ml). Although chest radiography was normal, chest CT showed enlarged nodes (para-aortic, aortopulmonary window area, **fig. 1**). Supraclavicular lymph node biopsy was performed and the histopathological examination revealed undifferentiated carcinoma. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) conducted after supraclavicular lymph node resection revealed positive accumulation in the mediastinal lymph nodes, but no other abnormalities (fig. 1). The patient was treated with 4 courses of CDDP/DOC chemotherapy. Shrinkage of the mediastinal and supraclavicular lymph nodes was noted on chest CT (fig. 1) and the serum CEA level also decreased from 11.6 to 2.1 ng/ml. The patient is still alive, 68 months to date, after the chemotherapy.

Case 2

A 55-year-old man was hospitalized because of precordial pain and fever in January 2006. He was diagnosed as having pericarditis based on the presence of pericardial effusion, elevated T waves in leads V_1–V_6 on the electrocardiogram and the presence of serum markers of inflammation (C-reactive protein, CRP). However, subcarinal lymph node enlargement was observed on chest CT and he was referred to our hospital. The patient had a history of smoking (70 pack-years). Physical examination revealed no abnormal findings, except the high fever. Enlargement of the subcarinal lymph node was observed on chest CT and the node was found to be positive on FDP-PET (**fig. 2**). Marked elevation of the serum level of soluble interleukin (sIL)-2 was noted (2,070 U/ml); however, other tumor marker levels were within normal ranges. Since transbronchial aspiration cytology failed to yield an exact histological diagnosis, lymph node resection was performed via video-associated thoracoscopic surgery (VATS). The histological findings revealed that large atypical cells with clear nucleolus proliferated solidly with neutrophil infiltration and lymphoid follicle formation. The immunological staining showed that cytokeratin (CK) markers (CK7, CK22, CK5/6 and CAM5.2) were positive, whereas CD3, CD5, CD20 and CD30 were negative, which confirmed the presence of an undifferentiated carcinoma. Based on results of the general physical and other examinations, the patient was diagnosed as having CUP. However, the serum markers of inflammation and elevated soluble IL-2 levels were persistent and the fever also persisted postoperatively. The patient was then treated with 2 courses of CDDP/DOC chemotherapy. The fever resolved after the chemotherapy, along with decrease of the serum CRP and sIL-2 (0.02 and 439 U/ml, respectively). Since the chemotherapy, the patient has remained disease-free and asymptomatic for 31 months to date.

Case 3

A 66-year-old man was followed at our hospital after left lower lobectomy for lung cancer (squamous cell carcinoma, SCC) in September 2001. He gave a history of smoking (40 pack-years) prior to the operation. The serum CEA rose to 4.4 ng/ml in June 2006. Chest radiography and CT revealed upper mediastinal lymph node enlargement, and FDG-PET showed positive accumulation in the node; however, no other abnormalities were detected (**fig. 3**a). There were no abnormalities on physical

examination either. A needle biopsy of the node was performed and the findings were consistent with undifferentiated carcinoma, which was apparently different in histology from that of the previously diagnosed pulmonary SCC. He was diagnosed as having CUP and was treated with 2 courses of CDDP/DOC chemotherapy plus concurrent thoracic radiotherapy (60 Gy/2 Gy × 30 fractions). The node was found to have reduced in size on chest radiography and CT (fig. 3b), and the elevated serum CEA level also decreased from 11.5 to 1.7 ng/dl.

In all 3 patients, detailed medical histories, thorough physical assessments, including laboratory investigations (blood analysis, urinalysis, stool occult blood test), bronchoscopy, upper and lower gastrointestinal studies, and CT of the brain, neck, abdomen and pelvis failed to identify the primary site of the cancer. The chemotherapy cycles were repeated every 3–4 weeks. All 3 patients are still alive without any sign of disease relapse on serial tests, including tests for tumor markers and radiographic examinations. The disease-free survivals were 68 months in Case 1, 31 months in Case 2 and 29 months in Case 3.

Discussion

Neither standard nor optimal chemotherapeutic regimens have yet been determined because of the complex and heterogeneous presentations of patients with CUP. Historically, the empiric approach, including platinum-containing regimens, has yielded response rates of between 30 and 40% and the median survival time has been reported to be approximately 8 months [1, 2]. Among the new agents which became available in the 1990s, the taxanes were reported to show significant activity against CUP. Based on the results of several studies [7–9] and 2 reviews [10, 11], it appears that platinum compounds plus taxanes may prove to be as effective or more effective than previous regimens. Our present cases treated with CDDP/DOC lend support to the notion that this regimen is active as empiric chemotherapy in patients with CUP, especially in cases with thoracic lesions.

In addition, all 3 cases exhibited prolonged disease-free survival after the chemotherapy. Follow-up of more than 1 year is not usually reported in prospective studies of CUP, but several studies conducted on small numbers of patients have demonstrated the patients to be alive and free of disease progression for several years. Hess et al. [3] summarized 1,000 consecutive cases of CUP and analyzed the relationship between the clinical features and survival. They demonstrated that CUP patients with 1 or 2 metastatic sites, but non-adenocarcinoma histology, and no liver, bone, adrenal or pleural metastasis, had the longest median survival time of 40 months. Greco et al. [8] also showed that although the median survival time was only 9.2 months, the 5-year survival rate was 10%. Thus, there have been long-term survivors among patients with CUP [12]. In addition, the predominant site of tumor metastasis was mediastinal lymph nodes in our cases. It was reported by Greco et al. [10] that responses to chemotherapy varied depending on the organs/sites of CUP and that the response rates were higher in patients with lymph node metastases than those with involvement of other organs (liver, bone, lungs). Although the differences in response rates among patients with different locations of the metastatic lymph nodes remain to be clarified, our experience suggests that CDDP/DOC is a useful chemotherapeutic regimen for CUP patients with thoracic lymph node involvement.

Riquet et al. [6] reported several CUP cases with metastatic thoracic lymph node involvement and suggested that long-term survival could be obtained by resection of the nodes in certain cases. In the present series, Case 2 underwent thoracic lymph node resection, but this did not result in normalization of the serum markers of inflammation. The subsequently administered CDDP/DOC chemotherapy, however, effectively reduced

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the levels of these markers. Thus, we consider that the adjuvant chemotherapy with CDDP/DOC to have been useful for controlling the disease in Case 2.

In addition to CDDP/DOC chemotherapy, concurrent thoracic radiotherapy was performed in Case 3. Both CDDP and DOC may be expected to exert considerable synergistic interactions with concurrent radiotherapy [13, 14]. Thus, concurrent radiotherapy could be undertaken with the administration of chemotherapeutic agents as radiosensitizers. Furthermore, the radiosensitizing effect of DOC is 10 times higher than that of paclitaxel at equimolar concentrations [15]. Thus, we believe that combined chemoradiotherapy can contribute to a better outcome and that radiotherapy may be a valuable therapeutic tool for locally advanced disease in patients with CUP, especially in those with thoracic metastases. In regard to the risk of the combined modality therapy contributing to the development of radiation pneumonitis, it has been shown that CDDP and DOC administration is feasible [14] and well-tolerated in lung cancer patients. Thus, this regimen may also be useful with concurrent radiotherapy for treating thoracic involvement in patients with CUP.

It has been demonstrated that FDP-PET scanning is useful for detecting unknown primary sites in patients with CUP and/or can serve as an additional diagnostic tool in CUP patients [16, 17]. Although FDG-PET failed to locate the primary sites in our cases, this examination should be carried out to diagnose patients with CUP. In addition, the information from FDG-PET scanning in our cases was valuable for selecting the appropriate therapeutic strategies in Cases 2 and 3. Surgical resection and radiotherapy were performed based on the disease locations revealed by FDG-PET in these cases. Thus, FDG-PET has a beneficial impact on therapeutic management [18] and may even allow a specific chemotherapeutic regimen to be selected for the target organ in patients with CUP. Further evaluation of this new diagnostic tool in this context is, therefore, warranted.

In summary, we have described herein 3 cases of CUP who responded well to combined modality therapy, including CDDP/DOC chemotherapy, and have shown prolonged disease-free survival.

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Fig. 1. Chest CT before chemotherapy showing enlarged mediastinal lymph nodes, and FDG-PET revealing positive accumulation in the mediastinal lymph nodes (Before). After four cycles of CDDP/DOC chemotherapy, shrinkage of the nodes was seen (After) in Case 1.

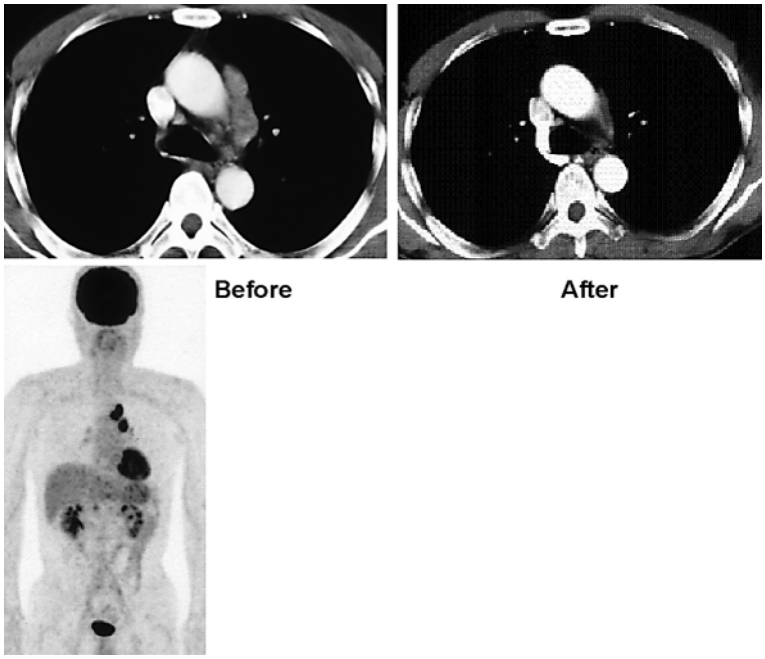

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Fig. 2. Chest CT showing enlargement of a subcarinal lymph node, and FDG-PET showing strong accumulation in the subcarinal lymph node (Before). After the lymph node resection and two cycles of CDDP/DOC chemotherapy, no accumulation of FDG-PET was observed (After) in Case 2.

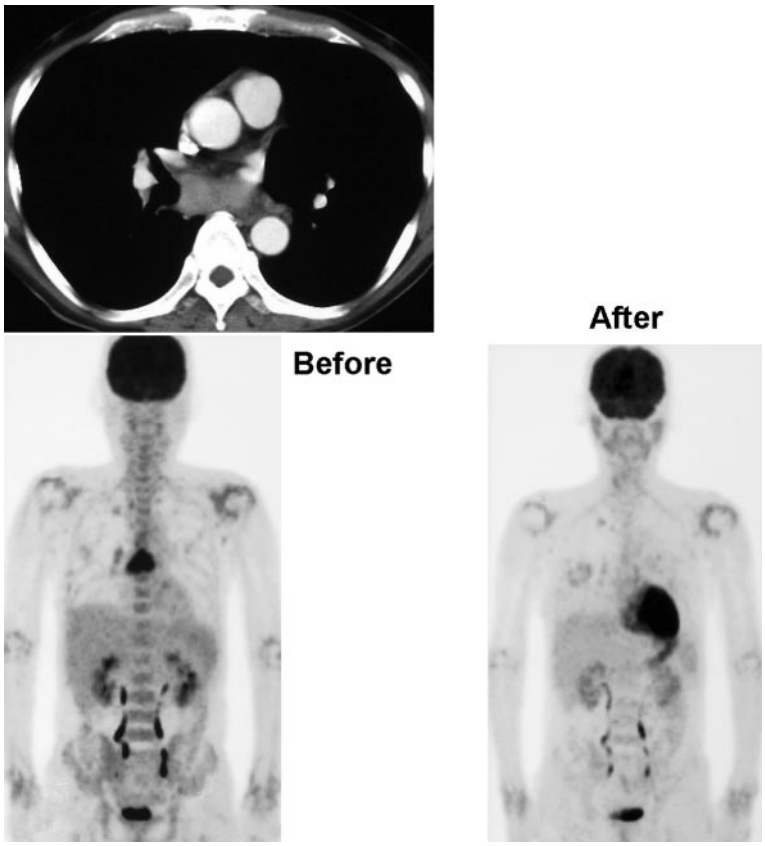

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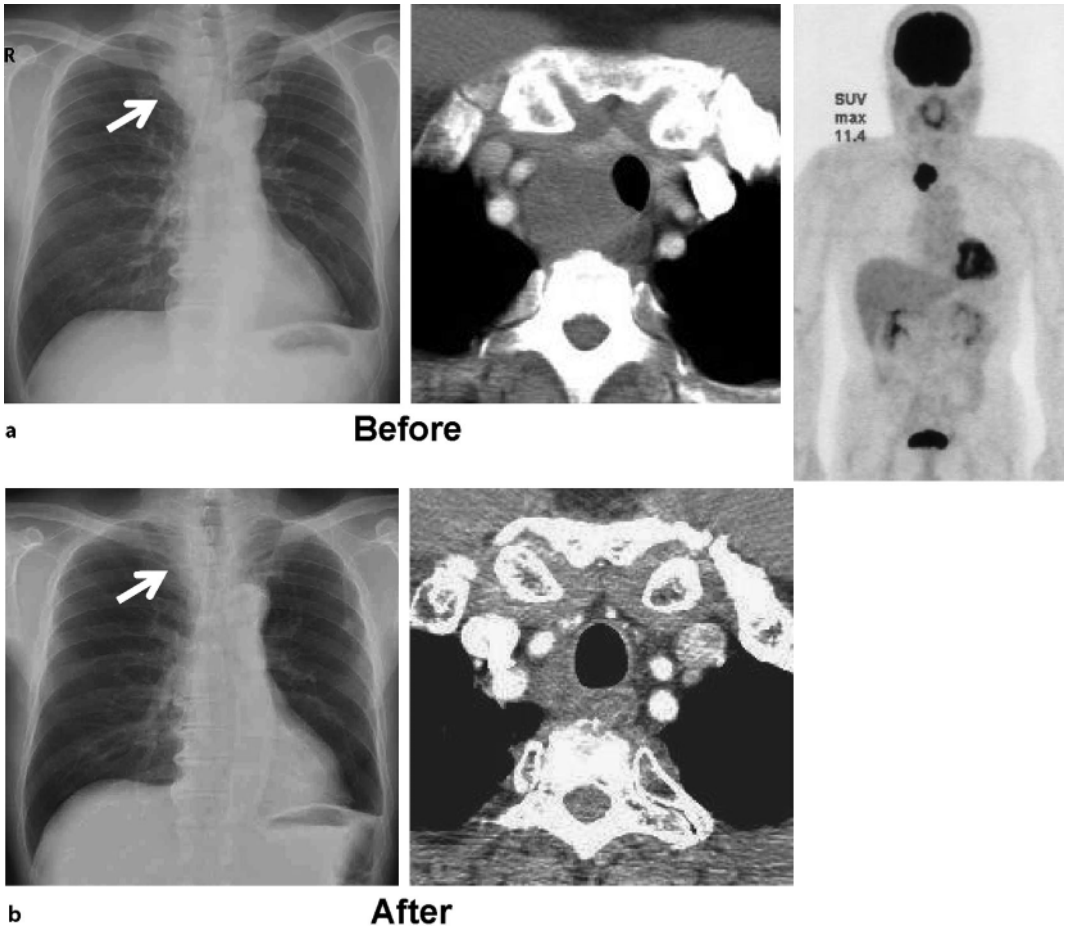
Fig. 3. **a** Chest radiograph, CT and FDG-PET before chemotherapy showing upper mediastinal lymph node enlargement in Case 3. **b** Chest radiograph and CT showing shrinkage of the lymph node after 2 cycles of CDDP/DOC chemotherapy with concurrent thoracic radiotherapy in Case 3.



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