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Editorial

Prognosis of Patients with Paraneoplastic Syndromes Associated with Lung Cancer

Nobuhiro Kanaji*

Department of Internal Medicine, Division of Endocrinology and Metabolism, Hematology, Rheumatology and Respiratory Medicine, Kagawa University, Japan

***Corresponding author:** Nobuhiro Kanaji, Department of Internal Medicine, Division of Endocrinology and Metabolism, Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Kagawa University, 1750-1 Ikenobe, Miki-cho, Kita-gun, Kagawa 761-0793, Japan

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Editorial

Recent accumulating evidence has shown the influence of paraneoplastic syndromes on the survival of patients with lung cancer. This short review article focuses on the prognosis of patients with a variety of paraneoplastic syndromes associated with lung cancer (Tables 1 and 2), and describes the reported survival rates in a concrete manner.

Paraneoplastic endocrine syndromes

Among the paraneoplastic endocrine syndromes, the three most common syndromes are humoral hypercalcemia of malignancy (HHM), syndrome of inappropriate antidiuretic hormone secretion (SIADH), and Cushing's syndrome [1]. Patients with these syndromes were reported to have a poor prognosis.

HHM: The majority of HHM cases are caused by secretion of parathyroid hormone-related protein (PTHrP) by tumor cells. HHM is usually found in individuals with a significant tumor burden [1]. The median survival time (MST) of 59 patients with hypercalcemia was 3.8 months, which was significantly shorter than that of patients without hypercalcemia (9.5 months, $p<0.001$) [2]. An even shorter MST (only 27 days) was also reported [3]. Another study showed that patients with serum PTHrP levels of >150 pmol/L (n=16) were associated with shorter survival (MST: 1.4 vs. 5.4 months, $p<0.015$) [4].

SIADH: SIADH is the major cause of hyponatremia in small cell lung cancer (SCLC) patients. Patients with SCLC and hyponatremia have a shorter survival than patients with normal serum sodium levels [5-7]. In an analysis of 453 patients with SCLC, the MST was 11.2 months in patients with normal sodium levels, compared with 7.1 months in patients with hyponatremia ($p=0.0001$) [5]. Hyponatremia in patients with extensive disease (ED) -SCLC was identified as an independent poor prognostic factor ($p=0.012$; relative risk: 1.31) [6]. In addition, it was reported that failure to normalize hyponatremia by chemotherapy was associated with poorer survival [5,7].

Cushing's syndrome: Most patients with Cushing's syndrome caused by SCLC had ED with a short MST (4 months) [8]. In a study of 454 patients with SCLC, 23 patients (4.5%) had Cushing's syndrome. The response rate to chemotherapy was only 46%, and the MST was only 3.57 months [9]. In another study of 840 patients with SCLC, 14 patients (1.6%) who exhibited ectopic ACTH production had a similar poor response rate (21%) and MST (5.5 months) [10].

Paraneoplastic hematologic syndromes

Paraneoplastic hematologic syndromes are often asymptomatic and usually detected after the diagnosis of cancer, typically with advanced disease [11], and are associated with a poor prognosis.

Tumor-related leukocytosis (neutrophilia): The MST of 33 patients with tumor-related leukocytosis was remarkably shorter than that of patients with leukocytosis caused by infection or bone marrow metastasis (4.6 vs. 15.5 months, $p<0.005$) [12]. Another study also showed a significant difference in survival between patients with and without leukocytosis (1.9 vs. 9.5 months, $p<0.001$) [2]. In a pooled analysis of more than 1000 patients, leukocytosis was found to be a significant negative prognostic factor for overall survival in patients with advanced-stage non-small cell lung cancer [13]. In addition, the MST of patients with hypercalcemia and leukocytosis was significantly shorter than that of patients with hypercalcemia alone (1.5 vs. 3.8 months, respectively) [2].

Thrombocytosis: Thrombocytosis is usually defined as a platelet count exceeding 400,000/mm^3. The survival of patients with thrombocytosis was reported to be significantly shorter than that of patients without thrombocytosis [14–16]. In a study of 611

Table 1: Paraneoplastic syndromes related to poor prognosis

Endocrine syndromes
Humoral hypercalcemia of malignancy (HHM)
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Cushing's syndrome
Hematologic syndromes
Tumor-related leukocytosis (Neutrophilia)
Thrombocytosis
Excessive eosinophilia*
Coagulopathy
Trousseau's syndrome

*Not fully established in lung cancer.

Table 2: Paraneoplastic syndromes related to prolonged prognosis

Neurologic syndromes
Lambert-Eaton myasthenic syndrome (LEMS)
Positive for anti-Hu antibody
Positive for anti-collapsing-response mediator protein 5 (CRMP5) antibody*
Dermatologic syndromes
Bazex syndrome*

*Not fully established.

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patients with lung cancer, the MST of patients with and without thrombocytosis was 7.5 and 10.1 months, respectively (p=0.0029) [14]. Multivariate analyses indicated that thrombocytosis was an independent prognostic factor [14,15].

Paraneoplastic coagulopathy

Trousseau's syndrome: Multiple definitions of Trousseau's syndrome can be found, ranging from the classic "occurrence of migratory thrombophlebitis with visceral cancer" to simply "carcinoma-induced coagulopathy" or "malignancy-related thromboembolism" [16,17]. Poor survival of patients with Trousseau's syndrome in lung cancer was reported [18,19]. The MST after onset of thromboembolism was 22.4 weeks [18]. The risk of dying after a venous thrombotic event was increased by three-fold [19].

Paraneoplastic neurological syndromes

A favorable prognosis was reported for Lambert-Eaton myasthenic syndrome (LEMS). The MST of patients with SCLC with LEMS (n=15) and without LEMS (n=81) was 17.3 and 10 months, respectively (p=0.048) [20]. Another study also reported that patients with LEMS (n=4) showed a longer survival (24.5 vs. 7 months, p=0.02) [21]. In addition, patients positive for anti-VGCC antibodies had a longer MST than antibody-negative patients (19.6 vs. 8.9 months) [22].

The presence of anti-Hu antibodies (Hu-Ab) was associated with limited disease stage (59.3% vs. 38.6%, p=0.047), complete response to therapy (55.6% vs. 19.6%, p<0.001), and longer survival (14.9 vs. 10.2 months, p=0.018) [23]. Moreover, spontaneous regression of SCLC with Hu-Ab without treatment was reported, suggesting an immune response directed against both the cancer and the nervous system [24-26]. Interestingly, a significantly longer MST was also reported in patients with SCLC and collapsing-response mediator protein 5 (CRMP5) -Ab (n=21) compared with that of patients with Hu-Ab (n=196) (52.5 vs. 11.53 months, p=0.01) [27]. However, another study reported no difference in survival between CRMP5-positive and -negative patients [28]. Additional studies are needed to determine how CRMP5-Ab affects the prognosis of SCLC. In almost 80% of patients, the paraneoplastic neurological syndrome antedates the diagnosis of lung cancer [29]. Early detection of an occult lung cancer has the potential to dramatically prolong survival. However, the symptoms of paraneoplastic neurological syndromes, such as confusion and dementia, may limit appropriate standard therapies for lung cancer, leading to shorter survival in some cases.

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