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Original article

Study of the clinicopathological features of soluble PD-L1 in lung cancer patients

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Abstract

Objective: In recent years, an association between serum soluble immune checkpoint molecules (sICMs) and malignant tumors has been reported, which may become important biomarkers in the future. Although several reports have suggested a correlation between sICMs and prognosis, their origin is unclear. In this study, changes in serum soluble PD-L1 (sPD-L1) during the perioperative period and its origin were analyzed in patients with lung cancer.

Patients and Methods: Patients with lung tumors (n=39) were included. Samples for sPD-L1 measurements were collected at five time points before and after surgery, and their changes over time were analyzed. ELISA was used to measure sPD-L1 levels.

Results: Thirty-nine patients with lung tumors (31, males; 8, females; age, 74 (years) ± 7.7 (range: 51–89) years; malignancy/benign, 33/6) were enrolled. Eight cases of driver gene mutation-positive tumors were included. Twenty-eight (72%) patients were smokers, and their performance status was 0-1 in all 39 patients. PD-L1 TPS was ≥50%/1–49%/<1% in 8/10/14 patients. Stage I/II/III/IV/postoperative recurrence of lung cancer was observed in 21/0/6/5/1 patients, respectively. There were no significant correlations between sPD-L1 levels and clinicopathological features and no correlation with PD-L1 TPS. Comparing localized lesions (stages I–III) with advanced lesions (stage IV and postoperative recurrence), the distribution of sPD-L1 was slightly higher in advanced lesions, although the difference was not significant. No obvious changes in sPD-L1 expression were observed before and after surgery.

Conclusion: sPD-L1 levels tended to be high in stage III and above lung cancer. There was no change in sPD-L1 levels before and after surgery. sPD-L1 levels did not correlate with the PD-L1 TPS.

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Introduction

Advanced/unresectable and recurrent lung cancers have a poor prognosis. According to statistics from the National Cancer Center Japan, such cancers are the number one cause of death by site in men and the second most common cause in women in Japan. Therefore, it is an epidemiologically important disease.

Lung cancer cells express immune checkpoint molecules such as PD-L1 (programmed cell death ligand 1), an immunosuppressive molecule, on the surface of the membrane. They bind to PD-1 (programmed cell death protein 1) expressed on the membrane surface of effector T cells responsible for tumor immunity and induce immune tolerance to tumors. Immune checkpoint inhibitors (ICIs) induce antitumor effects by inhibiting these immune checkpoints. Currently, multiple clinical trials[1, 2] have shown that the PD-L1 tumor proportion score (TPS) is associated with the response to ICIs and prognosis, and it is an important biomarker.

PD-L1 is present not only in tissues but also in the blood. In recent years, it has become possible to measure and quantify serum soluble immune checkpoint molecules (sICMs) such as sPD-L1, sPD-1, and sCTLA4. In addition, the relationships between sICMs and various malignant tumors

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have been studied, especially in other countries, and studies related to prognosis have been reported[3–7]. In the near future, they may become predictive biomarkers for response or prognosis, but currently, their origin and function remain unclear.

In this study, the clinicopathological characteristics, dynamics of changes in sPD-L1, and the origin of sPD-L1 were investigated in resectable lung cancers in the perioperative period. In addition, the correlation between PD-L1 and the glucocorticoid receptor (GR) which has recently been described in malignant tumors, has also been investigated. Some new findings are presented here.

Patients and Methods

At the Department of Thoracic Surgery of Tohoku Medical and Pharmaceutical University Hospital (Sendai, Japan), 40 patients were enrolled in prospective trials from December 2020 to July 2021, including patients scheduled for lung tumor surgery (including non-malignant tumors) and patients with unresectable or recurrent lung cancer. Written informed consent was obtained from all patients prior to the study. No treatment that would affect the sPD-L1 level, such as chemotherapy, was administered before surgery.

Materials

Peripheral blood samples (2.0 cc) were collected in EDTA-2K blood collection tubes and centrifuged at 3,000 rpm for 5 min. The plasma was separated, sealed in a microtube, and stored frozen at −80 °C. Samples were collected at five time points: before surgery, post-operative day (POD)1, POD7, POD14, and POD28.

Primary lung cancer was classified according to the 8th edition of the Lung Cancer Handling Regulations of the Japan Lung Cancer Society. For stage IV lung cancer, sPD-L1 data were collected only once before exploratory thoracotomy. For cases with a definitive pathological diagnosis of non-malignant disease, sPD-L1 was not sampled subsequently.

The following parameters were examined: sPD-L1 and clinicopathological features, including PD-L1 TPS, sex, age, BMI, smoking status, histological type, tumor diameter, gene mutation, tumor marker, stage, neutrophil count, total lymphocyte count, and steroid receptor (GR) expression. By analyzing the changes in sPD-L1 levels in the perioperative stage of resectable stage lung cancer, the origin of sPD-L1 in patients with lung cancer was investigated.

Immunohistochemical analysis

Surgical pathological specimens of the lungs of study subjects were immediately fixed with 10% buffered formalin after excision. Tissue specimens that were determined by two pathologists to have a sufficient number of tumor cells (100 or more viable tumor cells per field) in hematoxylin and eosin-stained sections were used. PD-L1 tumor proportion score (TPS) was measured by SRL (Tokyo, Japan), and immunohistochemical examination was performed using the 22C3 pharmDx assay (Dako North America, Carpinteria, CA, USA).

Immunostaining for glucocorticoid receptors of lung cancer specimens was performed at our facility.

sPD-L1 ELISA

Measurements were outsourced to an external company.

A two-step monoclonal antibody sandwich system was used to quantitatively measure the concentrations of sPD-L1 in human plasma using immunoassay reagents developed based on the HISCL-System (Sysmex, Hyogo, Japan).

Capture antibody (27A2) was presumed to have an epitope near the binding site of PD-L1 and CD80[24, 25]. Clone 130021 was used as the detection antibody.

Statistical analysis

Univariate analyses of the relationships between sPD-L1 and clinicopathological features and differences between the two groups were performed using Student's *t*-test. The correlation between the pStage and sPD-L1 was tested using the Kruskal–Wallis test.

JMP ver. 14.0 statistical software (SAS Institute, Cary, NC, USA) was used, with $P<0.05$ used to indicate a significant difference.

Results

Patients' characteristics

Forty patients were enrolled in the clinical trials, and 39 patients (male, 31 (79%); female, 8 (21%)) were included in the study. One patient was excluded from this study. Of the 39 patients, 38 underwent surgery, and one had recurrent lung cancer. The detailed patient characteristics are presented in Table 1.

The patients' age was 74 ± 7.7 (median 73, range: 51–89) years. Of the 39 cases, 34 (87%) were malignant tumors, of which 32 were non-small cell lung cancer (NSCLC), one was B-cell lymphoma, and one was small cell lung cancer (SCLC). Five patients (13%) had nonmalignant diseases. Non-malignant diseases included IgG4-related granuloma (n=1), non-tuberculous mycobacteria (NTM) (n=1); hamartoma (n=1), aspergilloma (n=1), and inflammatory nodule (n=1).

There were 28 smokers (current and former) (72%), and the median Brinkman index was 620 (range: 0–2,280). All subjects had an ECOG performance status of 0-1. The median BMI was 22 (range: 15–30) kg/m^2.

Of the 32 NSCLC cases, 20 were adenocarcinoma, and nine were squamous cell carcinoma; adenosquamous carci-

Table 1 Clinico-pathological characteristics

Patient population (n=39)			
			n (%)
Age	74 ± 7.7 (51–89)		39 (100)
Sex		Male	31 (79)
		Female	8 (21)
Histotype	Malignant tumor (34)	Adenocarcinoma	20 (51)
		Squamous cell carcinoma	9 (23)
		AdSQ	1 (2.6)
		LCNEC	1 (2.6)
		Pleomorphic	1 (2.6)
		B cell Lymphoma	1 (2.6)
		SCLC	1 (2.6)
	Non malignant disease (5)	Hamartoma	1 (2.6)
		Aspergilloma	1 (2.6)
		Inflammatory nodule	1 (2.6)
		Granuloma (IgG4)	1 (2.6)
		NTM	1 (2.6)
Smoking status		Smokers (currernt and former)	28 (72)
		Non smokers	11 (28)
Brinkman index	620 (range: 0–2280)		
ECOG PS		0-1	39 (100)
		≥ 2	0 (0)
BMI	22 (range: 15–30)		
pStage (NSCLC)	32	I	21 (65)
		II	0 (0)
		III	6 (19)
		IV	4 (13)
		Recurrence after surgery	1 (3)
Tumor diameter (mm) (NSCLC)	23 (12–100)		
Invasive diameter (mm) (NSCLC)	21 (7–100)		
Mutational status (NSCLC)	EGFR	19 Deletions	5 (16)
		21 L858R	2 (6)
		exon18	1 (3)
	Negative		24 (75)
	Others		0 (0)
PD-L1 TPS(%) (NSCLC)		≥50	8 (25)
		1–49	10 (31)
		< 1	14 (44)

noma (AdSQ), LCNEC, and pleomorphic carcinoma were one case each. Pathological stages I, II, III, and IV were seen in 21, zero, six, and four patients, respectively, and one patient had a recurrence.

The mean diameter of the invasive tumor and the overall tumor was 21 (7–100) mm and 23 (12–100) mm, respectively. Driver oncogene mutations were found in eight cases. All were EGFR gene mutations (19 deletions, 21L858R, and exon 18 in five, two, and one cases, respectively). The distribution of PD-L1 TPS (%) was 50–100 (high), 1–49 (low), and <1% (negative) in eight (25%), 10 (31%), and 14 (44%) cases, respectively.

sPD-L1 and clinicopathological features

Sample collections for sPD-L1 were planned at five time points (before surgery, POD1, POD7, POD14, and POD28); however, during the actual sample collection, a difference of several days occurred. The collection rates at the five time points were 100% (n=39), 49% (n=19), 33% (n=13), 38% (n=15), and 21% (n=8), respectively. In Stage I–III NSCLC (n=27) for which radical surgery was performed, the sample collection rates at the five time points were 100% (n=27), 67% (n=18), 44% (n=12), 56% (n=15), and 30% (n=8), respectively.

Table 2 shows the relationship between preoperative sPD-

Table 2 Relationship between preoperative sPD-L1 and clinicopathological features

Variables		n (%)	sPD-L1 (pg/mL) mean ± SD (range)	*P*-value
Age (years)	≥ 75	16 (41)	247 ± 128 (156–695)	0.22
	< 75	23 (59)	210 ± 58 (120–387)	
Sex	Male	31 (79)	234 ± 103 (120–695)	0.26
	Female	8 (21)	191 ± 24 (156–232)	
Smoking status	Never	11 (28)	198 ± 32 (156–267)	0.27
	current and former	28 (72)	235 ± 107 (120–695)	
BMI	≥ 22	18 (46)	186 ± 32 (120–248)	0.01
	< 22	21 (54)	259 ± 115 (171–695)	
Histology	Benign	5 (13)	178 ± 22 (150–211)	0.23
	Malignant	34 (87)	232 ± 98 (120–695)	
CRP (mg/dL)	≥ 1.0	6 (15)	241 ± 77 (178–387)	0.66
	< 1.0	33 (85)	222 ± 97 (120–695)	
Total lymphocyte count (/μL)	≥ 1,600	20 (51)	203 ± 46 (150–342)	0.15
	< 1,600	19 (49)	247 ± 123 (120–695)	
Neutrophil count (/μL)	≥ 4,000	18 (46)	218 ± 60 (160–387)	0.66
	< 4,000	21 (54)	231 ± 116 (120–695)	
Histology (Lung cancer, n=33)	NSCLC	32 (97)	216 ± 54 (120–387)	0.18
	SCLC	1 (3)	290	
Histology (NSCLC, n=32)	non-SQ	23 (72)	226 ± 57 (156–387)	0.04
	SQ	9 (28)	189 ± 37 (120–238)	
pStage (NSCLC, n=32)	I	21 (66)	209 ± 57 (120–387)	0.21
	II	0 (0)	–	
	III	6 (19)	215 ± 28 (178–238)	
	IV	4 (13)	264 ± 55 (211–342)	
	Recurrence after surgery	1 (3)	160	
Mutational status (NSCLC, n=32)	Positive	8 (25)	207 ± 40 (171–294)	0.63
	Wild type	24 (75)	218 ± 58 (120–387)	
Local or systemic lesion (NSCLC, n=32)	Local (Stage I–III)	27 (84)	210 ± 51 (120–387)	0.22
	Systemic (Stage IV and recurrence)	5 (16)	243 ± 67 (160–342)	
Tumor diameter (cm) (Stage I–III, n=27)	≥ 2.0	17 (63)	198 ± 32 (120–238)	0.09
	< 2.0	10 (37)	232 ± 70 (171–387)	
Invasive diameter (cm) (Stage I–III, n=27)	≥ 2.0	15 (56)	196 ± 34 (120–238)	0.1
	< 2.0	12 (44)	228 ± 64 (171–387)	
PD-L1 TPS (NSCLC, n=32)	<1%	14 (44)	222 ± 37 (171–294)	0.29
	1–49%	10 (31)	228 ± 77 (156–387)	
	50–100%	8 (25)	190 ± 42 (120–256)	

Univariate analyses of the relationships between sPD-L1 and clinicopathological features and differences between the two groups were performed using Student's *t*-test. The correlation between pStage and sPD-L1 was tested using the Kruskal–Wallis test.

L1 levels and clinicopathological features. No significant correlations were found with age, sex, smoking, histology, CRP level, or total lymphocyte/neutrophil count in all cases (n=39). The sPD-L1 level was significantly lower in patients with BMI ≥22 kg/m^2 (186 ± 32 (120–248) pg/mL) than in patients with BMI <22 kg/m^2 (259 ± 115 (171–695) pg/mL; *P*=0.01) (Table 2). One case of SCLC was included; however, there was no significant difference in the sPD-L1 levels between SCLC (290 pg/mL) and NSCLC (*P*=0.18). In addition, one patient with B-cell lymphoma of the lung was included and the patient had relatively high sPD-L1 levels (695 pg/mL).

For NSCLC (stages I–IV), no clear increase in sPD-L1 value was observed even in the late stage (*P*=0.21), and no correlation with gene mutation was observed (Table 2). Comparing local lesions, there was no significant difference in sPD-L1 levels between localized lesions (stage I–III: median 200 pg/mL) and systemic lesions (stage IV and recurrence: median 248 pg/mL) (*P*=0.22) (Figure 1). No significant correlation was found with the tumor diameter.

sPD-L1 and PD-L1 TPS

The correlation between sPD-L1 and PD-L1 TPS is shown in Table 3.

No significant correlation was found between sPD-L1 (before surgery) and PD-L1 TPS in NSCLC (stages I–IV) and localized NSCLC (stages I–III) (Figure 2).

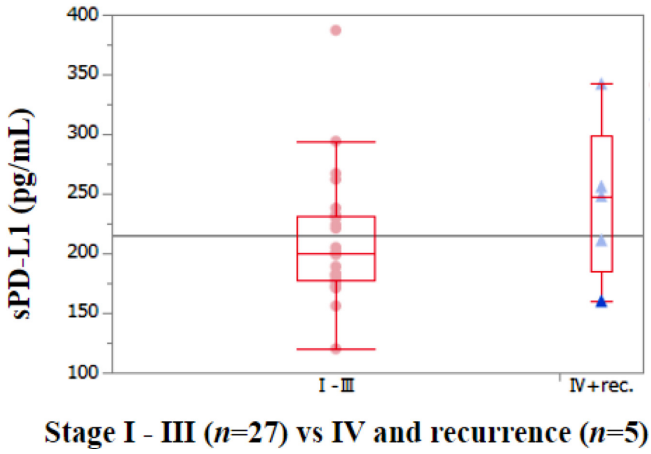

Figure 1 Correlation between sPD-L1 (before surgery) and stage. *P*=0.22.

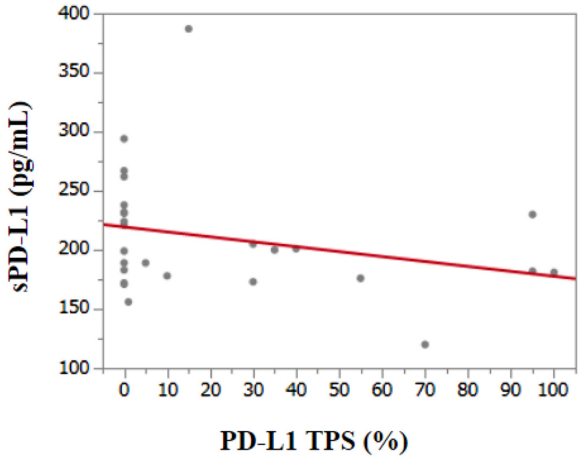

Figure 2 Correlation between sPD-L1 (before surgery) and PD-L1 TPS (NSCLC, localized lesion, stage I–III (n=27)). r =−0.27, *P*=0.17.

Table 3 Correlation between sPD-L1 and PD-L1 tumor proportion score

	n	PD-L1 TPS (%) median (range)	sPD-L1 (pg/mL) mean ± SD (range)	r	*P*-value
NSCLC (Stage I–IV)	32	5 (0–100)	216 ± 54 (120–387)	–0.24	0.2
NSCLC (Stage I–III)	27	0 (0–100)	210 ± 51 (120–387)	–0.27	0.17

Table 4 Changes in sPD-L1 in 27 patients who underwent radical surgery for localized NSCLC Stage I–III

		n	sPD-L1 (pg/mL) mean ± SD (range)
1	Before surgery	27	210 ± 51 (120–387)
2	1 POD	18	198 ± 48 (146–312)
3	7 POD	12	220 ± 46 (156–313)
4	14 POD	15	230 ± 59 (123–339)
5	28 POD	8	238 ± 72 (154–378)

Changes in sPD-L1 levels

Table 4 shows the changes in sPD-L1 levels in 27 cases in which radical surgery was performed for local lesions (Stage I–III) of NSCLC at five time points. No obvious change in sPD-L1 expression was observed before and after surgery (Figure 3).

Relationship between GR and PD-L1 or sPD-L1

For localized lesions of NSCLC (Stage I–III, n=21), tissue samples were stained with GR (immunohistochemistry; IHC), and the degree of GR expression and its correlation with PD-L1 TPS and sPD-L1 were examined. GR was expressed in all 21 cases, 1–49% in five cases (24%), and ≥50% in 16 cases (76%). A significant correlation was found between GR and PD-L1 TPS (*P*=0.04) (Table 5, Figure 4a, 4b).

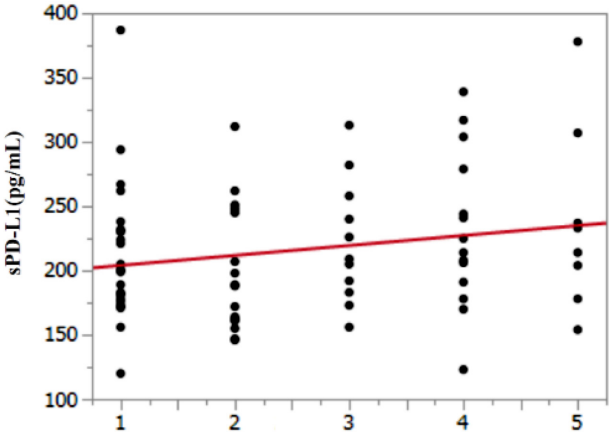

Figure 3 Changes in sPD-L1 in patients who underwent radical surgery (n=27); 1: before surgery; 2–5: after surgery. *P*=0.076.

Discussion

Cancer immunotherapy, including ICIs, is evolving rapidly. As the number of treatment options increases, so does the search for biomarkers. PD-L1 TPS requires tissue specimens obtained by bronchoscopy, biopsy, or surgery, and involves an invasive procedure. In the future, a minimally invasive and useful biomarker that can be collected from

Table 5 Relationship between GR and PD-L1 tumor proportion score and sPD-L1

GR (%)	n (%)	PD-L1 TPS (%) range	*P*-value	sPD-L1 (pg/mL) mean ± SD (range)	*P*-value
1–49	5 (24)	0–10	0.04	203 ± 42 (156–262)	0.71
≥ 50	16 (76)	0–100		211 ± 34 (172–294)	

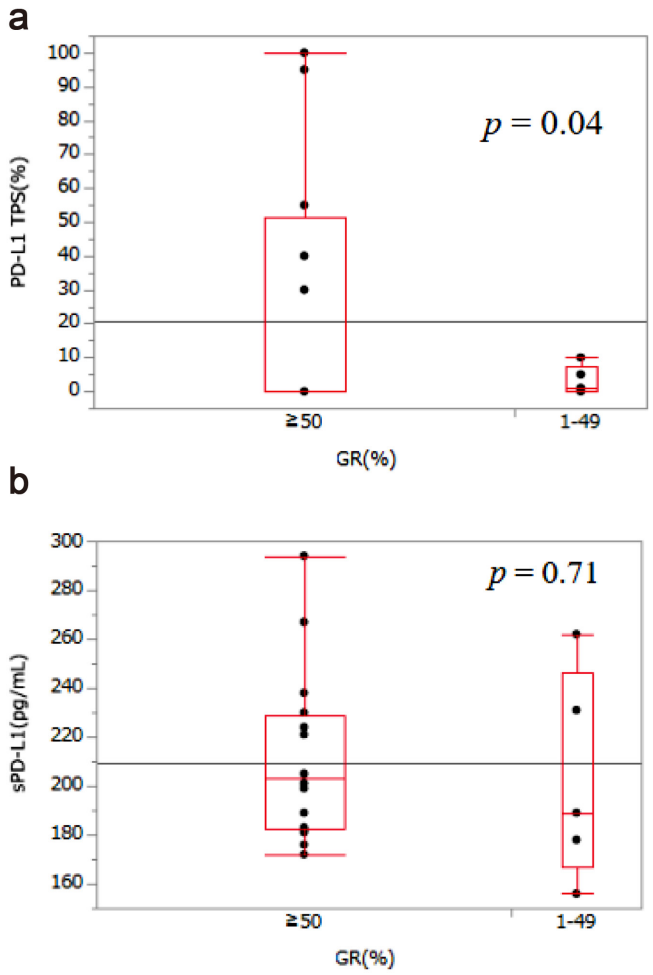

Figure 4 GR expression and PD-L1 TPS (4-a) or sPD-L1 (4-b) for localized NSCLC (Stage I–III, n=21).
GR was expressed in all 21 cases, with 1–49% in five cases (24%) and ≥50% in 16 cases (76%). A significant correlation was found between GR and PD-L1 TPS (*P*=0.04).

peripheral blood (liquid biopsy), such as sPD-L1 examined in this study, and that can predict the response to drug treatment and prognosis would be desirable.

The key feature of the present study was the follow-up and analysis of changes in sPD-L1 levels over time during the perioperative period in patients with resectable lung cancer.

General information regarding sPD-L1

PD-L1 is expressed not only on cancer cells, but also on lymphocytes, dendritic cells (DCs), macrophages, and the membrane surface of vascular endothelial cells[4]. It has a molecular weight of 33 kDa[8]. In recent years, blood-soluble immune checkpoint molecules (such as sPD-1, sPD-L1/2, and sCTLA4) have become measurable. Their relationships with not only lung cancer but also breast cancer, pancreatic cancer, rectal cancer[9], lymphoma[10], and various other malignant diseases have been reported in Japan and other countries. They are detected not only in patients with cancer but also in healthy people[6, 11–13] and patients with diseases other than cancer, such as rheumatoid arthritis, autoimmune hepatitis, and pulmonary fibrosis[5]. They are detected not only in the blood but also in pleural fluid[14].

Several previous reports have shown that sPD-L1 does not correlate positively with clinicopathological features such as age, sex, smoking status, histological type, and driver mutation in lung cancer patients[4, 11, 15–17]. However, there have been some reports of correlations between poor PS[3] and higher sPD-L1 values in adenocarcinoma[18].

sPD-L1 value correlates with progression-free survival (PFS) and overall survival (OS)[3–7]; the higher the value of sPD-L1, the worse the OS and PFS. In addition, when sPD-L1 levels increase during treatment, the response to ICI treatment and prognosis are poor[7, 19].

In the present study, sPD-L1 expression and BMI were significantly correlated (*P*=0.01). BMI has been reported to be associated with ICI response[20] and may be indirectly involved with sPD-L1 and ICI response.

The measured value of sPD-L1 in the present study

Since the measurement of sPD-L1 is not standardized, the measured values and units differ depending on each report. The results of the present study were not significantly different from those reported by Goto *et al.*[12] using the same measurement system.

In addition, lung cancer showed a high level of approximately 200 pg/mL, whereas lymphoma showed approximately 695 pg/mL. In the case of lymphoma, there is no contradiction even if the sPD-L1 value increases significantly because the number of neoplastic lymphocytes increases systemically, which has been reported in the literature[10]. However, it is interesting that the present study

showed high levels of lymphoma in intrapulmonary nodular lesions.

The origin of sPD-L1

The origin of sPD-L1 has been described in several studies. In addition to cancer cells, immunocompetent cells such as lymphocytes, activated dendritic cells[4, 21], and myeloid-derived suppressor cells (MDSCs)[6] have been considered. However, the nuances of the ratio of cancerous tissue to non-cancerous tissue with respect to the origin differ depending on the report. There has also been a report that proves that dendritic cells produce sPD-L1 *in vitro*[21], but none has been confirmed in lung cancer patients.

Increased tumor burden may increase sPD-L1 proportionally[4]; it is significantly correlated with tumor diameter[11] and is high in cases with lymph node metastasis or liver metastasis[3, 4]. At the site of metastasis, the sPD-L1 level tends to increase proportionally (but not significantly)[17]. These reports indicate that sPD-L1 is derived from cancer cells. However, there are multiple reports that there is no significant difference in sPD-L1 levels between healthy controls and lung cancer patients[6, 11, 17], and it is not necessarily derived only from cancer tissue.

When cancer becomes systemic or the tumor burden increases, the number of immune checkpoint molecules derived from the tumor and the number of lymphocytes infiltrating the tumor may increase, and the sPD-L1 level may increase.

Preoperative sPD-L1 in the present study showed no significant difference between local and systemic lesions, and there was no significant difference between malignant and benign lesions (Table 2, P=0.22). In addition, the changes in sPD-L1 were followed at five time points from before and after surgery in 27 cases where radical surgery was performed for Stage I–III NSCLC (Table 4, Figure 3), and no obvious change in sPD-L1 levels was observed. These results suggest that sPD-L1 may be derived from tissues other than tumor tissue. However, these levels may be affected by perioperative inflammation. For confirmation, it will be necessary to follow up with the group that underwent radical surgery for a long period of time on a yearly basis and to investigate the changes in sPD-L1 values.

It has been reported that the sPD-L1 protein is not homogenous, and its structure differs depending on whether it is derived from tumor or non-tumor-derived proteins[26]. If tumor-derived sPD-L1 can be identified clinically, the usefulness of sPD-L1 will increase.

Do sPD-L1 and PD-L1 TPS correlate in lung cancer patients?

It is necessary to consider whether the lung cancer is localized or systemic; however, it is considered that sPD-L1 collected from peripheral blood and PD-L1 TPS measured from lung cancer tissue do not correlate. Although there have been some reports of a weak correlation[4], there are many reports of no correlation[6, 11]. No clear correlation was found in this study also (Table 3, Figure 2). PD-L1 TPS is heterogeneous depending on the tissue collection site[22], and it is assumed that sPD-L1 also originates from tissue other than cancer, as described above. IHC findings of individual cancer tissue and plasma values are difficult to correlate.

The benefit of sPD-L1

Since sPD-L1 can be tested in the peripheral blood (liquid biopsy), it can be collected more easily than tests that require invasiveness, such as biopsy and surgery. Because it is relatively easy to collect several times, it is easy to confirm its reproducibility. Unlike tissue samples, heterogeneity does not occur depending on the collection site.

Correlation between glucocorticoid receptor (GR) and PD-L1 TPS or sPD-L1

Traditionally, cancer and steroids have been closely associated. Yalan *et al.*[23] reported that GR was involved in PD-L1 expression in pancreatic cancer. The present study also showed a significant correlation (P=0.04) for the association between GR expression (IHC) and PD-L1 TPS. Since steroids have immunosuppressive activity, it cannot be ruled out that GR may correlate with the expression of PD-L1, which promotes the immune tolerance of tumors. However, since the expression of PD-L1 in cancer tissue is heterogeneous, it is only used as a reference. If GR is involved in PD-L1 expression in patients with lung cancer, it may be involved in the response to drug treatment (especially ICI treatment) and prognosis in lung cancer treatment. In the future, a larger sample size should be investigated.

Conclusion

sPD-L1 levels tend to be high in Stage III and above lung cancers. There was no change in sPD-L1 before and after surgery. sPD-L1 levels do not correlate with PD-L1 TPS.

Study limitations

The study limitations were small cohort (n=39) and the changes in sPD-L1 levels may have been affected by perioperative inflammation.

Ethical considerations: This study was approved by the Institutional Review Boards of the Tohoku Medical and Pharmaceutical University Hospital (approval numbers: 2020-2-004, 2022-2-001-1). This study was conducted in accordance with the Declaration of Helsinki of the World

Medical Association and the ethical guidelines for human medical research.

Conflict of interest: The authors declare no conflict of interest.

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