Lung adenocarcinoma expressing receptor for advanced glycation end-products with primary systemic AL amyloidosis: a case report and literature review

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Abstract

Background: Receptor for advanced glycation end-products (RAGE), a receptor for amyloids, is constitutively expressed in lungs and generally observed to be downregulated in lung cancer tissues. However, increasing levels of RAGE or serum amyloids is associated with poor outcome in lung cancer patients. We report a rare case of primary systemic amyloid light-chain (AL) amyloidosis in biopsy-proven multiple organs with early-stage non-small cell lung cancer (NSCLC) that displayed strong staining for RAGE in the tumour tissue. Interestingly, compared with randomly selected lung cancer biopsy samples, including all representative histological subtypes of NSCLC and small-cell lung cancer, only the NSCLC in the present case showed strong expression for RAGE that can bind amyloids.

Case presentation: A 71-year-old woman was admitted to our hospital for comprehensive investigation of nephrotic syndrome. Computed tomography showed a small nodule in the right upper lung lobe with hilar mediastinal lymph node enlargement. Pathological examination of transbronchial biopsy samples of the nodule yielded a diagnosis of lung adenocarcinoma. Furthermore, the pathological detection of amyloid deposition in biopsy samples of a subcarinal lymph node, gastric and duodenal mucosa, cardiac muscle, and bone marrow led to a diagnosis of primary systemic AL amyloidosis with nephrotic syndrome and cardiomyopathy. In addition, RAGE was detected in lung tumour tissues surrounded by normal lung tissues with amyloid deposition.

Conclusion: The RAGE positivity of the lung cancer cells in this case suggests an interaction between amyloid-containing tissues and RAGE-expressing cancer cells. Lung adenocarcinoma with RAGE expression may be a complication of underlying amyloidosis.

Keywords: Amyloidosis, Case report, Lung adenocarcinoma, RAGE

Background

The incidence of systemic amyloidosis in patients with cancer is very rare and has been estimated to be between 0.1% and 0.4% among all cancers [1]. Increasing serum amyloid A (SAA) level in a patient with non-small cell lung cancer (NSCLC) is considered a predictive biomarker of poor prognosis [2]. Receptor for advanced glycation end-products (RAGE) is a transmembrane receptor of the immunoglobulin superfamily and binds structurally diverse molecules, including amyloids. RAGE is constitutively expressed in lungs and observed to be downregulated in lung cancer patients. RAGE associates with survival and metastatic spread of cancers [3, 4]. Herein, we report on a rare case of primary systemic amyloid light-chain (AL) amyloidosis in biopsy-proven multiple organs with early-stage NSCLC that displayed strong staining for RAGE in the tumour tissue.
Case presentation
A 71-year-old Japanese woman, non-smoker, with a history of cholelithiasis, hypertension, and dyslipidaemia, was referred to our hospital for evaluation of nephrotic syndrome. The patient had been diagnosed with hypertrophic cardiomyopathy 6 months previously.

On physical examination, the patient was 155.0 cm tall. She weighed 46.0 kg and showed a systolic ejection murmur from the left sternal border to the apex and pitting leg oedema. The remainder of the examination was unremarkable. On blood analysis, hypoalbuminemia (1.7 g/dL), proteinuria (4.5 g/gCr), and serum IgG M-protein were detected. Serum free light chain (SFLC) assay showed an increase in free lambda chain with a decreased kappa/lambda ratio (kappa SFLC: 7.8 mg/L, normal 3.3–19.4 mg/L; lambda SFLC: 70.5 mg/L, normal 5.7–26.3 mg/L; kappa/lambda ratio: 0.11, normal 0.3–1.3). On the other hand, SAA (5.6 μg/mL) and immunoglobulin were within normal limits. Creatinine (0.8 mg/dL), brain natriuretic peptide (325.8 pg/mL), and carcinoembryonic antigen (6.4 ng/mL) were elevated. Chest radiography showed a nodule, 2.1 cm in diameter, in the right upper lung field. Computed tomography revealed a nodule with marginal irregularity and bronchodilatation in the right upper lobe, hilar mediastinal lymph node enlargement, slight bilateral pleural effusion, pericardial effusion, and ascites (Fig. 1).

Pathological examination of transbronchial biopsy samples of the lung nodule yielded a diagnosis of adenocarcinoma (Fig. 2a). In addition, interstitial deposition of amorphous material that stained positively for Congo red with apple-green birefringence in the polarized view, and amyloid P component (Fig. 2h, i: duodenal mucosa; i, m: bone marrow). Only the subcarinal lymph node and the cardiac muscle stained positively for anti-lambda light chain antibodies. Furthermore, positive staining for RAGE was detected only in the lung tumour cells (Fig. 2b-e). The bone marrow demonstrated a normal population of plasma cells with slight atypia.

Finally, the case was diagnosed as lung adenocarcinoma, Stage IA (cT1bN0M0), and primary systemic AL amyloidosis with nephrotic syndrome and cardiomyopathy.

Because the patient displayed rapidly worsening edema and cardiac amyloidosis with elevated brain natriuretic peptide, she was given a poor prognosis rather than that expected with early-stage lung adenocarcinoma and was treated with dexamethasone (20 mg/day) and diuretics. The oedema, mainly due to the nephrotic syndrome with severe proteinuria, pleural effusion, and brain natriuretic peptide levels were not responsive to treatment. The patient died after 3 months despite dexamethasone and bortezomib treatment in another hospital.

Discussion
RAGE is a multiligand receptor that binds structurally diverse molecules, including high mobility group box 1, S100 family of proteins, some species of advanced glycation end-products, and β-sheet fibrillar material (e.g., amyloid-β and SAA). RAGE is constitutively expressed at high levels in alveolar-type cells and at relatively low levels in vascular endothelial cells, inflammatory cells, and neurons [4–6]. RAGE and its ligands are highly up-regulated in cancer tissue (e.g., pancreatic, colon, and prostate cancer) [7]. By contrast, both RAGE and serum

Fig. 1 Computed tomography (CT) images. a Chest CT scan showing the nodule with marginal irregularity and bronchodilatation in the right upper lobe. b CT scan in the mediastinal window showing mediastinal lymph node enlargement and bilateral pleural effusion.
soluble RAGE (sRAGE) levels are downregulated in smokers and lung cancer patients [7–9].

Interestingly, RAGE that can bind amyloids showed strong expression in primary lung adenocarcinoma tissue in the early stages (Fig. 2b) and negative expression in other amyloid-positive tissues without metastasis such as the subcarinal lymph node, duodenal mucosa, and bone marrow (Fig. 2c, d, e). We confirmed RAGE staining in lung cancer tissues without comorbidity of amyloidosis by applying immunohistochemical analysis in randomly selected biopsy samples of lung cancer, including all representative histological subtypes of NSCLC and small-cell lung cancer; these samples were used as the negative control (Fig. 3a-f).

Previous studies have reported that expression levels of RAGE and its ligands are associated with clinical outcome in patients with NSCLC. Upregulated RAGE expression and activity are associated with tumour invasion and

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Fig. 2 Microphotographs of the present case. a-b The lung adenocarcinoma (a, b, arrowheads): a haematoxylin and eosin staining (bar = 100 µm); b receptor for advanced glycation end-products (RAGE) staining (bar = 100 µm). Positive staining for RAGE is seen. c-e RAGE staining of other tissues (bar = 100 µm): c subcarinal lymph node; d duodenal mucosa; e bone marrow. None of these tissues show positive staining for RAGE. f-h Congo red staining (bar = 200 µm): f lung tissue surrounding the adenocarcinoma; g subcarinal lymph node; h duodenal mucosa; i bone marrow. Amorphous deposition was found in the tissues surrounding the tumour (f, arrowheads). j-m Amyloid P component staining (bar = 200 µm): j lung tissue surrounding the adenocarcinoma; k subcarinal lymph node; l duodenal mucosa; m bone marrow. All amorphous material shows positive staining for Congo red with apple-green birefringence in the polarized view, and amyloid P component

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Fig. 3 Immunohistochemical staining for receptor for advanced glycation end-products (RAGE) in control lung cancers: a solid adenocarcinoma; b acinar adenocarcinoma; c papillary adenocarcinoma; d lepidic adenocarcinoma; e squamous cell carcinoma; f small-cell carcinoma. All controls stained negatively for RAGE (bar = 100 µm)
metastatic activity in certain types of neoplasia, including gastric and colon cancer [10, 11]. In contrast, overexpressed RAGE in lung cancer cells suppresses tumour growth and the acquisition of cancer stem cell features in vitro [12]. sRAGE traps circulating ligands that are overexpressed in lung cancer and thus acts as an inhibitor of RAGE-mediated cell signalling [13]. We were not able to monitor the clinical time course of serum sRAGE level as a surrogate marker in this case. There is speculation that downregulation of both RAGE and sRAGE may be a critical step in the formation of lung tumours [8, 9, 14]. Several genetic single nucleotide polymorphism (SNP) studies identified that the SNPs in the RAGE associated with increased NSCLC risk and a lower chemotherapy response rate and poor prognosis [9, 15, 16]. In addition, increasing concentrations of SAA corresponded to poor response to tyrosine kinase inhibitors and correlated with poor clinical outcome [2, 17]. In the present patient, the onset of lung cancer appeared to match mostly with that of systemic AL amyloidosis with increasing SFLC, regarded as the precursor form of amyloid protein [18]. This case was not AA amyloidosis but systemic AL amyloidosis; thus, SAA levels were within normal limits.

The relationship between cancer and amyloidosis is still unknown, as well as the relevance of amyloidosis as a paraneoplastic syndrome induced by lung cancers. However, 10 of 12 case reports, including the present case, showed the diagnosed period of lung cancer to be the same as or prior to that of amyloidosis (Table 1) [19–29]. These clinical time courses suggest the prior onset of lung cancer may contribute to the deposition of amyloid through paraneoplastic mechanisms. In the present case, the deterioration of cardiac amyloidosis directly led to death, as a poorer prognostic factor than early lung cancer itself. Generally, RAGE levels are downregulated in lung cancer patients. However, our case showed strong expression of RAGE that was surrounded by lung tissue with amyloid deposition, even though the patient had early-stage lung cancer (Fig. 2b, f).

Thus, the RAGE positivity of lung cancer cells in this case suggests an interaction between amyloid-containing tissues and RAGE-expressing cancer cells, which may progress both lung cancer and amyloidosis. Further study is warranted to investigate this association.

### Conclusion

We describe a rare case of amyloid receptor-positive lung adenocarcinoma with systemic AL amyloidosis. Clinicians should be aware that RAGE-positive lung cancer may be a complication of underlying amyloidosis that could impact more severely on the prognosis of the patient than the cancer itself.

### Abbreviations

AL: Amyloid light-chain; NSCLC: Non-small cell lung cancer; RAGE: Receptor for advanced glycation end-products; SAA: Serum amyloid A; SFLC: Serum amyloid light-chain amyloidosis, BM bone marrow, C colon, CCRT concurrent chemoradiotherapy, D duodenum, F female, H heart, K kidney, L lung, LN lymph node, M male, N/A not available, NSCLC non-small cell lung carcinoma, SCC squamous cell carcinoma, SCLC small-cell lung cancer, SP spleen, ST stomach, y years

| Author, year | Age(y)/sex | Cancer type and stage | Amyloid organ involvement | Type | Prior diagnosis | Treatment for lung cancer | Cause of death |
|--------------|------------|-----------------------|---------------------------|------|----------------|---------------------------|----------------|
| van Bronswijk et al. 1982 [19] | 71/M | SCLC, Advanced | K | AA | Lung cancer | Radiotherapy | Pulmonary infection |
| Meyrier et al. 1985 [20] | 59/M | SCC, TbN1Mx | A, K, SP | AA | Lung cancer | CCRT | Renal failure due to amyloidosis |
| Focan et al. 1985 [21] | 70/M | SCC, Early | BM, Digestive tract | N/A | Unknown | None | Pulmonary infection |
| Richmond et al. 1990 [22] | 72/M | SCC, Early | Multiple organs | AA | Same | None | Peritonitis and Renal failure due to amyloidosis |
| Benharroch et al. 1992 [23] | 51/F | AC, N/A | F | AL | Unknown | None | Renal failure due to systemic sclerosis |
| Partidge et al. 2000 [24] | 69/M | NSCLC, Stage IV | Mediastinal LN | N/A | Same | None | NSCLC |
| Garthwhite et al. 2003 [25] | 64/M | SCC, N/A | K, L | AA | Same | Radiotherapy | N/A |
| Barcelo et al. 2003 [26] | 33/M | SCC, Stage IIIb | C, K | AA | Lung cancer | Chemotherapy | Pulmonary infection |
| Paydas et al. 2005 [27] | 50/M | AC, Stage IIb | K | AA | Lung cancer | CCRT | N/A |
| Miyazaki et al. 2011 [28] | 60/M | AC, Stage IA | K, L, ST | AL | Same | Surgery | N/A |
| Gueutin et al. 2013 [29] | 56/M | AC, Stage IIIb | K | AA | Lung cancer | Chemotherapy | N/A |
| Our case 2016 | 71/F | AC, Stage IA | D, H, K, L, ST | AL | Same | None | Heart failure due to amyloidosis |

* 'Same' refers to a diagnosis given at the same time as amyloidosis

**Table 1** Clinicopathological features of lung cancer patients with amyloidosis

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**Conclusion**

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free light chain; SNP: Single nucleotide polymorphism; sRAGE: soluble receptor for advanced glycation end-products

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Availability of data and materials
All data generated or analysed during this study are included in this published article.

Authors’ contributions
SO, IN, and TS collected the clinical data and drafted the manuscript. TS and KT revised the manuscript. SO, YK, JI, and YN carried out the clinical management of the patient. TU carried out the pathological diagnosis. KS and TU carried out immunohistochemical staining. All authors have read and approved the manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Juntendo University Graduate School of Medicine, Tokyo, Japan. 3Junior Resident of Juntendo University Hospital, Tokyo, Japan. 4Department of Pathology, Labor Health and Welfare Organization Kanto Rosai Hospital, Kanagawa, Japan.

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