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CASE REPORT

Serum KL-6 for diagnosis of ovarian carcinoma associated with dermatomyositis: two case reports and characteristic clinicopathological factors

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Abstract Patients with dermatomyositis have a predisposition to the development of malignant tumors. The incidence of ovarian carcinoma, especially, is higher in patients with dermatomyositis than in the general population. Recently, it was reported that serum levels of KL-6 (Krebs von den Lungen-6) may be elevated in patients with dermatomyositis associated with ovarian carcinoma. Herein, we describe two cases of ovarian carcinoma associated with dermatomyositis. The first patient was a 46-year-old woman with stage Ib serous papillary adenocarcinoma of the ovary. At the time of diagnosis, she had a 13-year history of dermatomyositis, and an elevated serum KL-6 level. Reduction of the serum KL-6 level was noted after resection of the tumor. Immunohistochemistry revealed positive staining of the tumor for KL-6. The other case was a 58-year-old woman with stage IV ovarian carcinoma who also had a history of dermatomyositis. She was initially started on chemotherapy, which resulted in shrinkage of the tumor and reduction of the serum KL-6 level. Surgery was then performed for resection of the tumor, and the chemotherapy was continued. However, the patient died of cancer 1 year and 4 months after the start of the treatment. For patients with dermatomyositis and with elevation of the serum KL-6 level in the absence of severe interstitial pneumonia, associated ovarian malignancy should be ruled out.

Keywords Ovarian carcinoma · Dermatomyositis · KL-6

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Introduction

Dermatomyositis is associated with a threefold increase in the risk of development of malignancies. For women with dermatomyositis the risk of ovarian carcinoma is increased 8 to 16-fold [1, 2]. KL-6 (Krebs von den Lungen-6), one of the markers of interstitial pneumonia, has been reported to be increased in cases of ovarian carcinoma to a greater degree than that expected with pneumonia activity [3–8]. Herein, we describe two cases of dermatomyositis diagnosed as having ovarian carcinoma, focusing on KL-6, and consider possibilities for early detection of ovarian carcinoma in these patients.

Case reports

Case 1

A 46-year-old woman, gravida 1, para 1, who had a 13-year history of dermatomyositis, was referred to our hospital to begin immunosuppressant drug treatment for her worsening interstitial pneumonia. When she first visited our department for further examination to rule out gynecological malignancies, she was recovering from pneumonia. She had no gynecological symptom other than hypermenorrhea and was found to have an intramural myoma measuring 10 cm in diameter and a left ovarian tumor measuring 5 × 5 × 2 cm in size on pelvic examination and magnetic resonance imaging (MRI). The laboratory test results were: serum carbohydrate antigen 125 (CA125), 143 U/ml; carbohydrate antigen 19-9 (CA19-9), 88 U/ml; serum KL-6, 1,650 U/ml (normal range, <500 U/ml). Suspecting an ovarian malignant tumor, we performed bilateral salpingo-oophorectomy with total hysterectomy

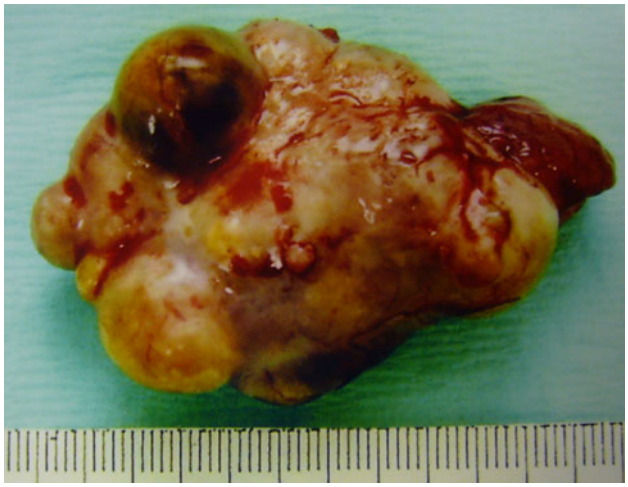

Fig. 1 The left ovarian serous papillary adenocarcinoma in case 1 patient

and partial omentectomy, without leaving behind any residual macroscopic tumor. Because of pre-existing restrictive ventilatory impairment caused by the interstitial pneumonia, lymphadenectomy was omitted. The tumor was diagnosed as a FIGO stage Ib serous papillary adenocarcinoma of the left ovary (Fig. 1).

On the basis of reports of KL-6 expression in ovarian cancer tissues, we performed an immunohistochemical examination for this case. It revealed that the tumor cells stained positively for KL-6 (Fig. 2a, b).

After the operation, serum levels of CA 125, CA19-9, and KL-6 all decreased. Currently, 2 years and 4 months after the surgery, the patient remains free from carcinoma recurrence and deterioration of dermatomyositis.

Case 2

A 58-year-old postmenopausal woman, gravida 2, para 2, was referred to our department because of a newly detected pelvic mass and massive pleural effusion with adenocarcinoma cells of the right thorax. She had been diagnosed with dermatomyositis associated with interstitial pneumonia at age 56 and had received steroid and immunosuppressant drug treatment. The pelvic mass was 13 × 11 × 9 cm in size, and the ultrasonographic and MRI findings strongly suggested the presence of a malignant ovarian tumor. Serum CA125 and KL-6 were elevated to 8,306 and 4,930 U/ml, respectively, whereas serum CA19-9 was within normal limits. The tumor was diagnosed as a stage IV primary ovarian carcinoma. Malignant cells were detected in a peritoneal fluid cytology examination. For treatment of the pleural effusion, she received 4 cycles of combined chemotherapy with paclitaxel (175 mg/m^2) and carboplatin (AUC 5.0). Evaluation after the chemotherapy revealed shrinkage of the tumor and reduction of the serum CA125 and KL-6 levels. Bilateral salpingo-oophorectomy with total hysterectomy and partial omentectomy was performed. Lymphadenectomy was omitted because of preoperatively widely spread cancer cells. Microscopic examination revealed residual cancer cells at the site of the left ovarian tumor (7 × 4 × 2.5 cm in size). An immunohistochemical examination for KL-6 was performed, but we could not achieve clear staining because of profound necrosis (Fig. 2c, d). Although she was administered 2 more cycles of chemotherapy with paclitaxel and carboplatin after surgery, increases of the serum levels of CA125 and KL-6 were detected. Under suspicion of a platinum-refractory tumor, the regimen of the chemotherapy was changed to single-agent docetaxel (70 mg/m^2). When the serum CA125 and KL-6 levels increased again after 4 cycles of docetaxel, followed by a 2-month break, a course of single-agent irinotecan hydrochloride (100 mg/m^2) was to be administered on a weekly schedule for 3 weeks, but the patient died of cancer 1 year and 4 months after the initial chemotherapy (Fig. 3). The symptoms of dermatomyositis had been kept stable only by oral prednisolone.

Discussion

Dermatomyositis is an autoimmune disease characterized by the appearance of distinctive skin lesions (heliotrope eyelids and Gottron's papules) and weakness of the proximal muscles. The incidence is estimated to be 1–2 cases per 100,000 population in Japan. Patients with the disease have an increased predisposition to the development of malignancies, interstitial pneumonia, polyarthritis, and Raynaud's phenomenon. Malignancies in these patients are also associated with poor prognosis [1, 2, 9, 10]. Kaneko et al. [11] reported that the leading cause of death in patients with dermatomyositis is malignancy (54.6%), followed by interstitial pneumonia (18.5%). Cherin et al. [12] reported that the rate of development of malignancy associated with dermatomyositis was as high as 13–19%. The main treatment for dermatomyositis is steroids and immunosuppressant drugs, and for patients with associated malignancy, antitumor therapy is also potentially effective against the dermatomyositis [10, 13–16].

The mechanism underlying the association of dermatomyositis and malignancy is unknown, but the following hypotheses have been proposed [17, 18]:

1. The skin and muscle symptoms are caused by a hypersensitive reaction to the malignancy.
2. The skin and muscle symptoms are caused by some agent released by the malignant tumor.

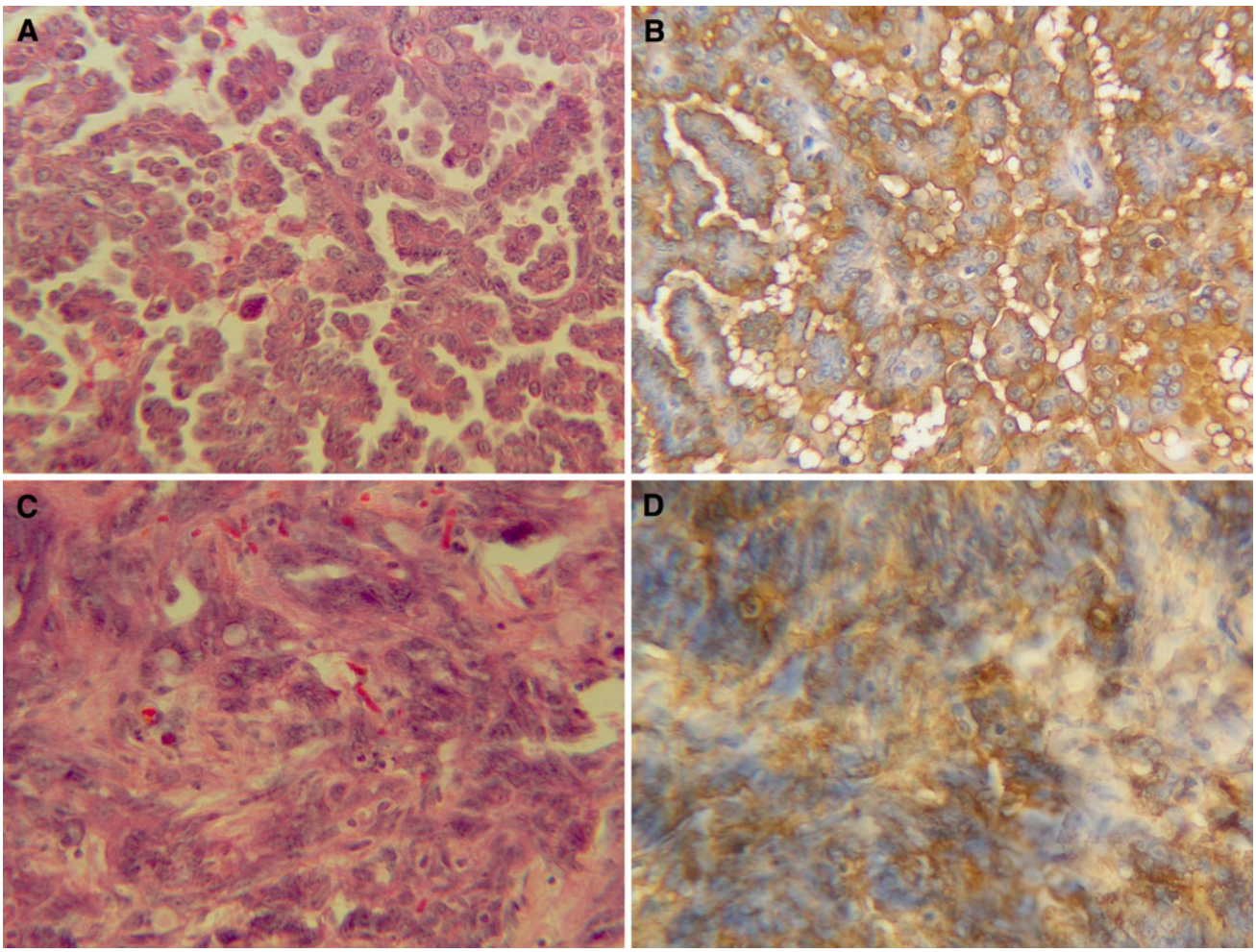

Fig. 2 Hematoxylin–eosin staining and immunohistochemical staining with anti-KL-6 antibody of the ovarian tumor of case 1 patient (**a**, **b**, respectively) and case 2 patient (**c**, **d**) at 200-fold magnification

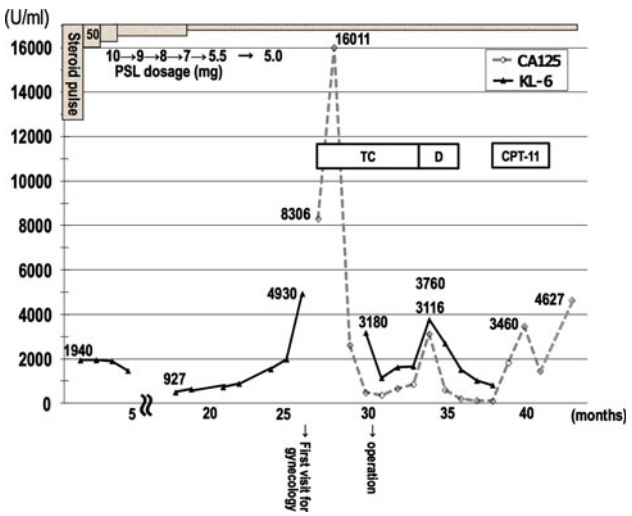

Fig. 3 The time course of case 2 patient after the first visit to our hospital. The KL-6 level, which was not tested during months 26–29 and 38, decreased substantially during the treatment. *TC* paclitaxel plus carboplatin, *D* docetaxel, *CPT-11* irinotecan hydrochloride

3. The skin and muscle symptoms and the malignancy are caused by an identical etiological agent (e.g. virus, changes in the immune system).
4. The malignancy is caused by the impaired immunity in association with dermatomyositis.

With regard to the most frequently encountered malignancies in patients with dermatomyositis, Hill et al. reported the following data: pulmonary carcinoma standardized incidence ratio (SIR) 3.7–9.2; total malignancies' SIR 2.5–3.6; pancreatic carcinoma SIR, 1.6–9.0; gastric carcinoma SIR, 1.7–7.3; colorectal carcinoma SIR, 1.4–4.4 [2]. In addition, incidence of ovarian carcinoma is significantly high (relative risk (RR) 8.2 (95% CI 2.7–19.2); total malignancy 3.4 (2.4–4.7) [1]; SIR 10.5 (6.1–18.1); total 3.0 (2.5–3.6) [2]) and is especially high in the 5 years after diagnosis of dermatomyositis (RR 16.7 (5.4–38.9); total malignancy 4.8 (4.3–9.0) [1]).

Because of the high incidence of associated malignancies, malignancy screening is recommended for patients

diagnosed with dermatomyositis [10, 12, 14]. Because of the significantly high the incidence of malignancies in the first 2 years, a report has recommended malignancy screening for 4–5 years after diagnosis of dermatomyositis [19].

In one of our cases, malignancy was diagnosed by screening, together with deterioration of dermatomyositis; in the other case, further evaluation of the patient's new symptom 2 years after diagnosis of dermatomyositis led to the diagnosis. The optimum screening method and reasonable frequency and duration of follow-up are still unclear.

KL-6 is one of the extracellular epitopes of MUC1 (polymorphic epithelial mucin), a transmembrane glycoprotein secreted by type II pulmonary epithelial cells and bronchial glandular cells. Kono et al. detected antibodies against the protein in 1985, and serum KL-6 has recently been reported to be a very useful marker for interstitial pulmonary disease. Furthermore, some reports have suggested that serum KL-6 may also be useful as a tumor marker for breast cancer, non-small-cell pulmonary carcinoma, colorectal carcinoma, and hepatocellular carcinoma, on the basis of observations of elevation of the serum KL-6 in patients with these cancers and recognition of KL-6 expression in their tissues [20–27].

With regard to serum KL-6 level in ovarian cancer patients, reports have been published on high KL-6 levels in ovarian cancer cases with dermatomyositis; in addition, Matsunaga et al. investigated the KL-6 status in 71 ovarian cancer patients without dermatomyositis. They reported serum KL-6 was elevated in 36% of the cases, with the levels being significantly higher in patients with stage III to IV carcinoma [9]. As for our cases, the serum KL-6 levels were not related to the activity of the interstitial pneumonia, but rather to the associated malignancy. In case 1, we also detected KL-6 expression in the cancer cells of the resected ovary. In both of our cases the course of serum KL-6 level was similar to that of CA125. However, their levels may have different trends, because they are epitopes of different types of MUC. KL-6 could be an important tumor marker in patients who are negative for the usually tested markers for ovarian carcinoma—CA125, CA19-9, and CEA. In addition, CA15-3, which is often tested in breast cancer cases, is also an epitope of MUC1, and one report suggests that CA15-3 could be an alternative marker for KL-6 in fibrotic lung disease [28]. In our cases, we did not evaluate CA15-3 levels or expression.

Here, we emphasize the importance of malignancy screening for patients with dermatomyositis who have significantly elevated levels of serum KL-6 that are disproportionate to the active level of interstitial pneumonia. Future studies on the usefulness of serum KL-6 as an ovarian tumor marker are warranted. Furthermore, because an antitumor effect of anti-KL-6 antibody against a breast cancer cell line has been reported, future use of KL-6 as a therapeutic target can be expected [29].

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Sigurgeirsson B, Lindelof B, Edhag O et al (1992) Risk of cancer in patients with dermatomyositis or polymyositis. A Population-based study. NEJM 326(6):363–367
2. Hill CL, Zhang Y, Sigurgeirsson B et al (2001) Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet 357:96–100
3. Uchida A, Sugihara M, Ito S et al (2006) Ovarian cancer with swelling of the right upper arm, amyopathic dermatomyositis, and elevated serum KL-6. J Jpn Soc Intern Med 95(4):130–132 (in Japanese)
4. Takashima A, Yasuda Y, Fukaya S et al (2005) Ovarian carcinoma associated with polymyositis &dermatomyositis: a case report. Kanto J Obst and Gyn 42:15–19 (in Japanese)
5. Oyama Z, Oda M, Seishima M et al (2004) Dermatomyositis with elevation of serum KL-6 level by ovarian carcinoma. Rinsyo Derma 46(2):249–251 (in Japanese)
6. Suzuki A, Sumigama S, Mizogami Y et al (2003) A case of ovarian carcinoma with dermatomyositis. Tokai J Obst and Gyn 40:61–69 (in Japanese)
7. Kodera M, Usuda T (2002) A case of dermatomyositis with significantly high level of KL-6 associatedwith ovarian cancer. Ryumachi 42(4):694–698 (in Japanese)
8. Arai S, Katsuoka K, Sekine A et al (2001) KL-6 level of a patient with dermatomyositis correlated with ovarian carcinoma activity: a case report (in Japanese). Jpn J Clin Dermatol 55(10):759–762 (in Japanese)
9. Matsunaga T, Hiraiwa Y, Kodaira H et al (2004) KL-6 is a useful tumor marker for ovarian cancer. Jpn J Gyn Oncol 22(3):235 (in Japanese)
10. Andras C, Ponyi A, Constantin T et al (2008) Dermatomyositis and polymyositis associated with malignancy: a 21-year retrospective study. J Rheumatology 35(3):1–7
11. Kaneko K, Kikuchi R, Arai Y et al (1985) Dermatomyositis and malignancies. Rinsyo Derma 27(5):499–505 (in Japanese)
12. Cherin P, Piette JC, Herson S et al (1993) Dermatomyositis and ovarian cancer: a report of 7 cases and literature review. J Rheumatol 20:1897–1899
13. Bonnetblanc JM, Bernard P, Fayol J (1990) Dermatomyositis and malignancy. Dermatologica 180:212–216
14. Callen JP (1982) The value of malignancy evaluation in patients with dermatomyositis. Am Acad Dermatol 6:253–259
15. Tanemoto T, Ishizuka Y, Houjyo M et al (2004) A case of recurrence ovarian cancer associated with dermatomyositis. Tokyo J Obst and Gyn 53(1):89–94 (in Japanese)
16. Hashimoto M, Yoshifuji H, Mimori T (2004) A case of dermatomyositis associated with different types of cancers at intervals of six years. Jpn J Clin Immunol 27(6):427–430 (in Japanese)
17. Saito Y, Odaka M, Sato S et al (2004) Clinicopathological study of resected and autopsied cases of lung cancer associated with dermatomyositis. Jpn J Lung Cancer 44(7):763–766
18. Takashina N, Kashiwazaki S (1990) Collagen diseases and malignancy. Medical Frontline 45(2):313–317 (in Japanese)
19. Wakata N (2000) Polymyositis and dermatomyositis accompanied with malignancy. Neurol Ther 17(6):539–545 (in Japanese)
20. Ishikawa N, Hattori N, Yokoyama A et al (2008) Usefulness of monitoring the circulating Krebs von den Lungen-6 levels to

predict the clinical outcome of patients with advanced nonsmall cell lung cancer treated with epidermal growth factor receptor tyrosine kinase inhibitors. Int J Cancer 122(11):2612–2620
21. Fujiwara Y, Kiura K, Toyooka S et al (2008) Elevated serum level of sialylated glycoprotein KL-6 predicts a poor prognosis in patients with non-small cell lung cancer treated with gefitinib. Lung Cancer 59(1):81–87
22. Inata J, Hattori N, Yokoyama A et al (2007) Circulating KL-6/MUC1 mucin carrying sialyl Lewisa oligosaccharide is an independent prognostic factor in patients with lung adenocarcinoma. Int J Cancer 120(12):2643–2649
23. Guo Q, Tang W, Inagaki Y et al (2006) Clinical significance of subcellular localization of KL-6 mucin in primary colorectal adenocarcinoma and metastatic tissues. World J Gastroenterol 12(1):54–59
24. Ogawa Y, Ishikawa T, Ikeda K et al (2000) Evaluation of serum KL-6, a mucin-like glycoprotein, as a tumor marker for breast cancer. Clin Cancer Res 6(10):4069–4072
25. Gad A, Tanaka E, Matsumoto A et al (2005) Assessment of KL-6 as a tumor marker in patients with hepatocellular carcinoma. World J Gastroenterol 11(42):6607–6612
26. Kurosaki M, Izumi N, Onuki Y et al (2005) Serum KL-6 as a novel tumor marker for hepatocellular carcinoma in hepatitis C virus infected patients. Hepatol Res 33(3):250–257
27. Tang W, Inagaki Y, Kokudo N et al (2005) KL-6 mucin expression in carcinoma of the ampulla of Vater: association with cancer progression. World J Gastroenterol 11(35):5450–5454
28. Kruit A, Gerritsen WBM, Pot N et al (2010) CA15-3 as an alternative marker for KL-6 in fibrotic lung diseases. Sarcoidosis Vasc Diffuse Lung Dis 27(2):138–146
29. Doi M, Yokoyama A, Kondo K et al (2006) Anti-tumor effect of the ani-KL-6/MUC1 monoclonal antibody through exposure of surface molecules by MUC1 capping. Cancer Sci 97(5):420–429