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The clinical application of tumor markers in the screening of malignancies and interstitial lung disease of dermatomyositis/polymyositis patients: A retrospective study

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Abstract

Objective: To examine the clinical utility of tumor markers in dermatomyositis/polymyositis patients in Taiwan.

Method: Data were collected retrospectively from the database of Taichung Veterans General Hospital in Taiwan from 1998 to 2014. Patients who fulfilled Bohan and Peter criteria of dermatomyositis/polymyositis were recruited. Serum level of tumor markers including carcinoembryonic antigen, alpha-fetoprotein, carbohydrate antigen 125, carbohydrate antigen 19-9 and carbohydrate antigen 15-3 were measured. The occurrence of malignancies and interstitial lung disease was identified. The association of tumor markers with malignancies and interstitial lung disease was examined using Chi-square test or Fisher's exact test.

Results: Among the enrolled 151 patients, 98 (64.9%) dermatomyositis and 53 (35.1%) polymyositis, a total of 15 malignancies were detected: breast ductal carcinoma (n = 4), bladder transitional cell carcinoma (n = 2), lung adenocarcinoma (n = 2), cervical intraepithelial neoplasia 3 and papillary squamous cell carcinoma (n = 2), colorectal (colon and rectal adenocarcinoma) (n = 2), uterine adenocarcinoma (n = 1), nasopharyngeal carcinoma (n = 1) and hematological malignancy (myelodysplastic with excess blast cells) (n = 1). Among the patients with malignancies, 13 (86.7%) had dermatomyositis, 2 (13.3%) polymyositis and 3 (20%) interstitial lung disease. The mean duration from dermatomyositis/polymyositis diagnosis to the occurrence of malignancies was 6.05 ± 5.69 years. There was no significant association of raised tumor markers with the occurrence of malignancies ($p > 0.085$), while a significant association was observed between the elevated levels of carbohydrate antigen 15-3 and the presence of interstitial lung disease ($p = 0.006$).

Conclusion: Tumor markers were not useful in malignancy screening or dermatomyositis/polymyositis patients in this tertiary center. The evaluation of the occurrence of malignancy in dermatomyositis/polymyositis patient should include a multidimensional approach. A raised level of carbohydrate antigen 15-3 may be a potential indicator of the presence of interstitial lung disease in dermatomyositis/polymyositis patients.

Keywords

Dermatomyositis, polymyositis, tumor markers, malignancy screening, interstitial lung disease, Taiwan

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Introduction

Dermatomyositis (DM) and polymyositis (PM) are the two main subtypes of idiopathic inflammatory myopathy. The association between DM/PM and malignancies has been well established.[1] Previous population-based studies showed standardized incidence ratio of malignancies to be higher in DM/PM patients than in normal population, with the malignancy risk greater in DM than in PM.[2] The most common malignancy associated with DM/PM varied in different geographical areas and ethnics, with nasopharyngeal carcinoma (NPC) the most common among DM/PM patients in China, Taiwan and Southeast Asian countries.[3–6] Contrary, the common malignancies associated with DM/PM in European countries were colon, lung and ovarian cancer.[7–9]

To date, there is no consensus on the screening for malignancies in DM/PM. Suggested surveys for malignancies included computed tomography (CT) of the thorax, abdomen and pelvis, mammography, gynecological examination and nasopharynx assessment.[4,8,10,11] A more advanced imaging, positron emission tomography/computer tomography (PET/CT) had shown its ability to detect occult malignancies in DM/PM patients; however, the ultimate diagnosis still needing histopathology confirmation.[12,13] The usefulness of tumor markers such as carcinoembryonic antigen (CEA), carbohydrate antigen 15-3 (CA15-3), carbohydrate antigen 19-9 (CA19-9) and carbohydrate antigen 125 (CA125) in detecting malignancies in DM/PM patients has been assessed. Although Amoura et al.[14] reported that CA125 and CA19-9 could be useful tumor markers, a more recent study did not show any association of these tumor markers with malignancies in DM/PM patients.[15] The utility of these tumor markers in screening for occult malignancies in DM/PM remains controversial. Myositis-specific autoantibodies (MSA) such as anti-transcriptional intermediary factor-1 gamma (anti-TIF1 γ), anti-nuclear matrix protein 2 (anti-NXP2) and anti-melanoma differentiation gene 5 (anti-MDA5) were reported to have an increased risk of malignancies in DM/PM patients.[16–18] However, these MSA were not easily available in Taiwan.

The incidence of interstitial lung disease (ILD) is notably higher than the incidence of malignancies in DM/PM patients. ILD may occur in up to 65% of DM/PM patients at diagnosis.[19] Therefore, a more promising marker to detect the occurrence of ILD is essential. Elevated tumor markers were observed in patients with ILD.[20–22] However, the clinical implication of tumor markers in relation to ILD is still ambiguous.

In view of the most prevalent malignancy associated with DM/PM in Taiwan was NPC, and there was no specific conventional tumor marker which can accurately detect or monitor this malignancy at present, we hypothesized that measuring these tumor markers may not be essential as part of malignancy screening for Taiwanese patients with DM/PM. To our knowledge, there is no previous study investigating the associations of tumor markers with the occurrence of malignancies or ILD in Chinese patients with DM/PM. Therefore, we aim to examine the usefulness of tumor markers in DM/PM patients in Taiwan.

Methodology

Data source

Data were collected retrospectively from the database of Taichung Veterans General Hospital, a tertiary medical center in Taiwan, using the Hyperion Enterprise Performance Management System (Oracle, Redwood City, CA, USA). DM/PM patients fulfilling the Bohan and Peter[23] criteria and diagnosed with *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) code for DM/PM (710.3 for DM and 710.4 for PM)[24] were identified from the hospital registry. This study was conducted in accordance with the Helsinki Declaration and was approved by the Institution Review Board of Taichung Veterans General Hospital, Taiwan (IRB number: CG13104-1). This retrospective cohort was a sub-study of a previous DM/PM study.[25] The written informed consents were obtained from all subjects prior to starting the study.

Study population

All adult DM/PM patients older than 18 years of age who possessed catastrophic illness certification for DM/PM in the period from 1 January 1998 to 31 December 2014 were recruited. To own the DM/PM catastrophic illness certification in Taiwan, patients must be evaluated by at least two experienced rheumatologists examining the detailed medical history, clinical symptoms, laboratory investigations and imaging. We excluded patients who had malignancies prior to the diagnosis of DM/PM. Patients who had not been checked for any serum tumor marker after the diagnosis of DM/PM were also not eligible for this analysis (Figure 1). PET/CT were not included in our study because the test is not routinely done. The cost of PET/CT is high in Taiwan, and it is not reimbursed by Taiwan National Health Insurance. MSA were also not reviewed in our study because these tests were not available during the recruitment period. The sample size was calculated using SamplePower software version 2.0 with alpha level set at 0.05 and the power set at 0.8. The minimal subjects required in malignancy and non-malignancy were 13 each, with the assumption of positive tumor markers in malignancy patients was 0.5 and in non-malignancy patients was 0.03.[14]

Tumor markers assays

Up to now, there is no protocol in malignancies screening for DM/PM patients locally and internationally. The tumor markers used in this cohort were all based on the clinician

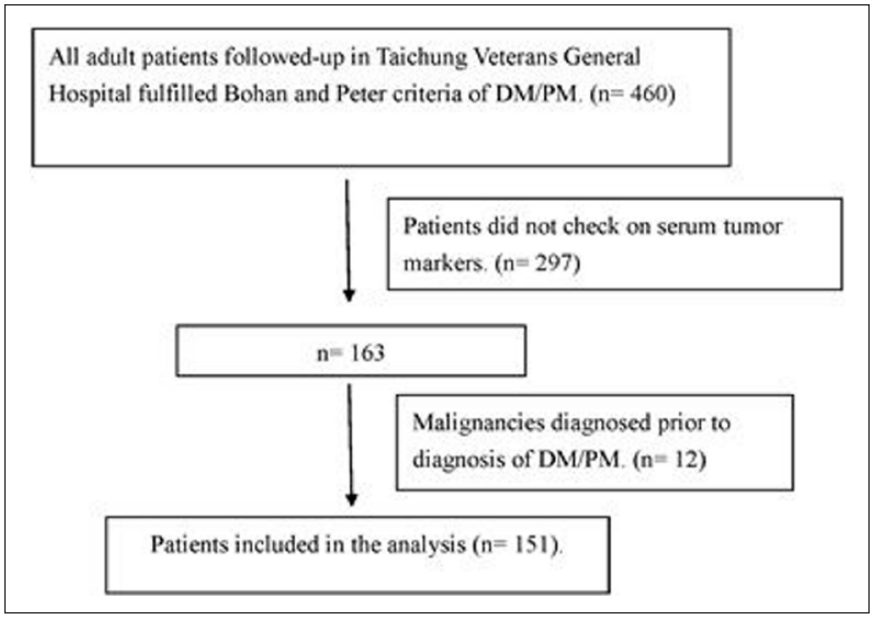

Figure 1. Flowchart of patients' selection in this hospital-based cohort study.

judgments. Tumor markers evaluated in this study were serum CEA, CA125, CA19-9, CA15-3 and alpha-fetoprotein (AFP) on the first sample taken within 1 month after the diagnosis of DM/PM. CA125, CA19-9 and CA15-3 were measured with the electro-chemiluminescence immunoassay of Roche Diagnostics Cobas e601 (Roche, Mannheim, Germany); CEA and AFP with an immunoradiometric assay kit (Cisbio Bioassays, Codolet, France). The normal ranges for tumor markers were CEA < 5.0 ng/mL, CA125 < 35.0 U/mL, CA19-9 < 34.0 U/mL, CA15-3 < 25 U/mL and AFP < 12 ng/mL.

Study outcome

The primary outcome was the detection of malignancies after the diagnosis of DM/PM. Malignancies were identified using ICD-9-CM (140.x–172.x, 174.x–195.8 and 200.x–208.x).[26] The diagnoses of malignancy were further confirmed by the histopathology evidence available. We also determined the occurrence of ILD (ICD-9-CM 515 and 516.3),[27] which was confirmed by the presence of abnormalities on high-resolution CT (HRCT) scan of the lung examined by well-trained radiologist blinded to the data of tumor markers. Abnormalities on HRCT of ILD included sub-pleural honeycombing, bronchiectasis, ground glass opacities, cryptogenic organizing pneumonia pattern, consolidation and pneumomediastinum.[28]

Statistical analysis

Demographic data were presented as mean ± standard deviation for continuous variables, and as number of cases and percentage in categorical variables. Chi-square test or Fisher's exact test was used in comparing the variables. Data were presented as odds ratio (OR) with 95% confidence interval (CI). Statistical Package for the Social Sciences (SPSS) version 22.0 software (SPSS, Chicago, IL, USA) was used to analyze the data. Significant p value was set at <0.05.

Results

Demographic data

In total, 151 patients were enrolled in this study (Figure 1). Of them, 98 (64.9%) were DM and 53 (35.1%) were PM patients. The majority of patients were female (65.6%). The mean age of the patients was 47.7 ± 13.6 years. A total of 368 tumor marker tests were done. The most commonly ordered tumor markers in this study were CEA and AFP with 26.6% and 26.1% respectively. Among the tumor markers done, only 13.3% showed elevated results.

The clinical utility of tumor markers in detecting malignancies

A total of 15 malignancies were detected in this study (Table 1). Among the patients with malignancies, 13 (86.7%) were DM and 2 (13.3%) were PM. The most common malignancy observed in this study was breast ductal carcinoma (n = 4) followed by bladder transitional cell carcinoma (n = 2), lung adenocarcinoma (n = 2), cervical intraepithelial neoplasia 3 and papillary squamous cell carcinoma (n = 2), colorectal carcinoma (colon and rectal adenocarcinoma) (n = 2), uterine adenocarcinoma (n = 1), NPC (n = 1) and hematological malignancy (myelodysplastic with excess blast cells) (n = 1).

Table 1. Demographic data and clinical characteristics of dermatomyositis (DM)/polymyositis (PM) patients with malignancies.

	Gender	Diagnosis	Age of diagnosis (years)	Cancer type	Cancer diagnosis interval (years)	Relevant tumor markers	Concomitant ILD
1	F	PM	52.5	Breast ductal carcinoma	11.14	CEA (–), CA15-3 (–)	No
2	F	DM	36.9	Breast ductal carcinoma	8.96	CEA (–), CA15-3 (–)	No
3	F	DM	45.5	Breast ductal carcinoma	5.71	CEA (–), CA15-3 (–)	No
4	F	DM	57.3	Breast ductal carcinoma	0.77	CEA (–), CA15-3 (–)	No
5	F	DM	56.5	Bladder transitional cell carcinoma	10.46	CEA (+)	No
6	M	DM	77.1	Bladder transitional cell carcinoma	2.35	NR	No
7	F	DM	45.2	Lung adenocarcinoma	3.59	CEA (–)	No
8	M	DM	44.1	Lung adenocarcinoma	0.04	CEA (+)	No
9	F	DM	25.8	Cervical intraepithelial neoplasia 3	4.38	CEA (–), AFP (ND)	No
10	F	DM	56.9	Cervix papillary squamous cell carcinoma	0.00	CEA (–), AFP (–)	No
11	F	DM	41.2	Uterine adenocarcinoma	0.97	CEA (–), AFP (–)	No
12	M	DM	55.3	Nasopharyngeal carcinoma	0.02	NR	Yes
13	F	DM	50.1	Rectal adenocarcinoma	16.89	CEA (–)	Yes
14	M	DM	56.7	Colon adenocarcinoma	14.58	CEA (+), CA19-9 (+)	No
15	F	PM	51.6	Myelodysplastic with blast cells	10.90	NR	Yes

F: female; M: male; ILD: interstitial lung disease; CEA: carcinoembryonic antigen; CA15-3: carbohydrate antigen 15-3; (–): negative; (+): positive; NR: not relevant; AFP: alpha-fetoprotein; ND: not done.

The mean age of malignancy diagnosed was 50.2 ± 11.6 years. Majority of the malignancies (60%) were detected more than 3 years after the diagnosis of DM/PM. The mean duration of occurrence of malignancies from DM/PM diagnosis was 6.05 ± 5.69 years. Among the patients with malignancies, three had concomitant ILD.

CA15-3. Among the 34 patients screened for CA15-3, 9 (26.5%) showed elevated results. None of these patients with elevated results developed a malignancy (p = 0.293; OR: 0.80; 95% CI: 0.66–0.97) (Table 2).

CA125. Of 71 patients tested for CA125, 18 (25.4%) showed positive results. Only a patient with positive result had malignancy (uterine carcinoma) (p = 1.000; OR: 1.50; 95% CI: 0.13–17.60).

CA19-9. Among 69 patients who were tested for CA19-9, 10 (14.5%) had elevated results. One of the patients with positive results developed malignancy (colon carcinoma) (p = 0.474; OR: 2.07; 95% CI: 0.19–22.19).

AFP. In total, 96 patients were tested for AFP, 4 (4.2%) showed elevated results. None of these patients with elevated results developed a malignancy (p = 1.000; OR: 0.96; 95% CI: 0.92–1.00).

CEA. In total, 98 patients were screened for CEA, 8 (8.2%) showed positive results. Of these patients with positive results, three developed malignancies (two lung carcinoma and one colon carcinoma) (p = 0.085; OR: 4.31; 95% CI: 0.90–20.59).

The clinical utility of tumor markers in detecting ILD

In this cohort, 61 (40.4%) patients developed ILD including 46 (75.4%) DM and 15 (24.6%) PM patients. The mean age of developing ILD was 49.0 ± 11.0 years. There were 28 (45.9%) of ILD detected within 1 year after the diagnosis of DM/PM. Anti-Jo1 antibody positivity was significantly associated with the presence of ILD (p < 0.001; OR: 10.15; 95% CI: 3.27–31.57). Among the patients who had elevated serum CA15-3, the majority (88.9%) developed ILD (p = 0.006; OR: 17.00; 95% CI: 1.81–160.05) (Table 3). Otherwise, tumor markers such as CA125, CA19-9, CEA and AFP showed no significant association with the presence of ILD.

Discussion

In this hospital-based cohort study of 151 DM/PM patients, we have observed 15 cases (9.9%) of malignancies; 13 (13.3%) with DM and 2 (3.8%) with PM. This observation was in agreement with the results from previous reports.[1,14] Compared to another population-based study,[3] our results showed a higher proportion of malignancies in DM. This discrepancy might be due to the patient selection criteria of the study that some patients were excluded, hence reduced the denominators of DM. There was no significant association of elevated tumor markers with the occurrence of malignancies in DM/PM patients (Tables 1 and 2), which was consistent with the results demonstrated by Andráás et al.[15] and supported by several international recommendations that tumor markers are not useful for malignancy screening.[29–33]

Table 2. The association of tumor markers and malignancies in dermatomyositis/polymyositis patients.[a]

Malignancy						Odds ratio (95% CI)
	No (n = 136)		Yes (n = 15)		p value	
	n	%	n	%		
Age (years)	47.4 ± 13.9		50.2 ± 11.6		0.448	
Gender					0.703	
Male	48	35.3	4	26.7		
Female	88	64.7	11	73.3		
CA15-3					0.293	
Negative	20	69.0	5	100.0		
Positive	9	31.0	0	0.0		0.80 (0.66–0.97)
CA125					1.000	
Negative	51	75.0	2	66.7		
Positive	17	25.0	1	33.3		1.50 (0.13–17.60)
AFP					1.000	
Negative	88	95.7	4	100.0		
Positive	4	4.3	0	0.0		0.96 (0.92–1.00)
CEA					0.085	
Negative	79	94.0	11	78.6		
Positive	5	6.0	3	21.4		4.31 (0.90–20.59)
CA19-9					0.474	
Negative	56	86.2	3	75.0		
Positive	9	13.8	1	25.0		2.07 (0.19–22.19)

CI: confidence interval; CA: carbohydrate antigen; CEA: carcinoembryonic antigen; AFP: alpha-fetoprotein.
p values were determined by Fisher's exact test.
[a]Values are mean ± standard deviation or the number (n) of patients.

American Society of Clinical Oncology stated that CEA is not recommended as a screening for colorectal cancer,[29] and there was insufficient data to suggest CA15-3 as a screening test for breast cancer.[30] Similarly, National Academy of Clinical Biochemistry (NACB) Laboratory Medicine Practice Guidelines did not recommend CEA, CA15-3 and CA125 testing as the screening for colorectal, breast and ovaries cancers, respectively.[31] According to American Association for the Study of Liver Diseases and the Asian Pacific Association for the Study of the Liver, AFP alone is also insufficient for the diagnosis of hepatocellular carcinoma.[32,33] However, opposed to our results, previous studies demonstrated a significant association of raised tumor markers with malignancies in DM/PM patients.[14,34,35]

Interestingly, CA15-3 level was significantly higher in many DM/PM patients, with its raised levels associated with a 17-fold risk of ILD (p = 0.006; OR: 17.00; 95% CI: 1.81–160.05). None of the ILD patients with elevated CA15-3 developed malignancy. These findings were consistent with the observation from previous studies that CA15-3 may be increased in patients with collagen-vascular diseases and ILD, but without occurrence of malignancy.[21,22] The employed monoclonal antibodies in CA15-3 assay recognized amino acids sequences on the central protein core of mucin-1.[21] The mucin-1 is a high-weight glycoprotein which is expressed on the surface of various epithelial cells such as type II pneumocytes,[36] hence explains the association of elevated CA15-3 levels with the presence of ILD. Krebs von den Lungen-6 (KL-6), an important serum marker used in detecting ILD, was also noted to be specific to mucin-1. Kruit et al.[37] demonstrated that both CA15-3 and KL-6 were equally sensitive and specific for pulmonary fibrosis associated with ILD. Although other studies had reported the association between ILD and other tumor markers such as CEA and CA19-9,[20,38] these associations were not observed in our study.

In the previous studies based on population from 1997 to 2007, the most common malignancy associated with DM/PM in Taiwan was NPC.[3,24] Increased awareness of the NPC risk such as betel nut chewing, smoking, consuming preserved food and the implementation of cancer screening program may help in reducing NPC incidence.[39] In contrast, the incidence of breast cancer showed a rising trend possibly due to the westernization of lifestyle in Taiwan.[40] These could probably explain the trend of the breast cancer replacing NPC as the most common malignancy associated with DM/PM patients in this study.

Our study has several limitations. First, the misclassification and misdiagnosis may occur; however, with the stringent criteria of catastrophic illness certification, the bias should be minimal as these patients would be reviewed thoroughly by the review board before the certificates were issued. Second,

Table 3. The association of tumor markers and interstitial lung disease in dermatomyositis/polymyositis patients.[a]

Interstitial lung disease						
	No (n = 90)		Yes (n = 61)		p value	Odds ratio (95% CI)
	n	%	n	%		
Age (years)	46.8 ± 15.2		49.0 ± 11.0		0.306	
Gender					0.116	
Male	36	40.0	16	26.2		
Female	54	60.0	45	73.8		
CA15-3					**0.006**	
Negative	17	94.4	8	50.0		
Positive	1	5.6	8	50.0		17.00 (1.81–160.05)
CA125					0.305[b]	
Negative	30	81.1	23	67.6		
Positive	7	18.9	11	32.4		2.05 (0.69–6.11)
AFP					1.000	
Negative	49	96.1	43	95.6		
Positive	2	3.9	2	4.4		1.14 (0.15–8.44)
CEA					0.273	
Negative	54	94.7	36	87.8		
Positive	3	5.3	5	12.2		2.50 (0.56–11.12)
CA19-9					0.737	
Negative	30	83.3	29	87.9		
Positive	6	16.7	4	12.1		0.69 (0.18–2.70)
Anti-Jo1					**<0.001**[b]	
Negative	72	94.7	39	63.9		10.15 (3.27–31.57)
Positive	4	5.3	22	36.1		

CI: confidence interval; CA: carbohydrate antigen; CEA: carcinoembryonic antigen; AFP: alpha-fetoprotein.
[a]Values are mean ± standard deviation or the number (n) of patients.
p values were determined by Fisher's exact test and [b]Chi-square test.
The bold values are significant p values.

the number of malignancy and ILD cases in our DM/PM patients may not represent the actual number if these diagnoses were made or the patients received treatment at other hospital. Third, owing to the lack of standardized malignancy screening protocol, missing data did exist. Moreover, the types/numbers of the tumor markers checked were not uniform in this retrospective study; this would cause bias in the data interpretation. The majority of excluded patients had not been checked for any tumor markers. The incidence of ILD seemed to be lower in the excluded group compared with the enrolled subjects (15.1% vs 40.1%). Therefore, the enrolled study population may overestimate the association of tumor markers and ILD in DM/PM patients. Fourth, the trend of malignancy observed in this study may not represent the trend in Taiwan as the data analyzed was not a population-based database. Therefore, an upcoming study looking for an up-to-date malignancy trend in DM/PM in Taiwan population is essential. Finally, the newer investigation modalities such as PET/CT, anti-TIF1 gamma, anti-MDA5, anti-NXP2 and KL-6 were not included due to their availability in Taiwan. A future study on these modalities together with the conventional markers should be compared in order to provide us more complete information.

Conclusion

In conclusion, we have demonstrated that tumor markers were not useful in malignancies screening for DM/PM patients in this tertiary center. Instead, the screening should comprise other investigation modalities such as examinations of the nasopharynx, gynecology, radiology or histopathology according to the clinical symptoms and the most prevalent malignancy in different geographical areas and ethnics. In addition, CA15-3 may be a promising indicator for detecting the presence of ILD in DM/PM patients, yet requires further confirmation by a larger and long-term study.

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and Y.-M.C. performed clinical assessments, statistical analysis and drafted the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from Institution Review Board of Taichung Veterans General Hospital, Taiwan (IRB number: CG13104-1).

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Informed consent

Written informed consents were obtained from all subjects before the study.

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References

1. Sigurgeirsson B, Lindelöf B, Edhag O, et al. Risk of cancer in patients with dermatomyositis or polymyositis. A population-based study. *N Engl J Med* 1992; 326: 363–367.
2. Zahr ZA and Baer AN. Malignancy in myositis. *Curr Rheumatol Rep* 2011; 13: 208–215.
3. Chen YJ, Wu CY, Huang YL, et al. Cancer risks of dermatomyositis and polymyositis: a nationwide cohort study in Taiwan. *Arthritis Res Ther* 2010; 12: R70.
4. Zhang W, Jiang SP and Huang L. Dermatomyositis and malignancy: a retrospective study of 115 cases. *Eur Rev Med Pharmacol Sci* 2009; 13: 77–80.
5. Leow YH and Goh CL. Malignancy in adult dermatomyositis. *Int J Dermatol* 1997; 36: 904–907.
6. Tang MM and Thevarajah S. Paraneoplastic dermatomyositis: a 12-year retrospective review in the Department of Dermatology Hospital Kuala Lumpur. *Med J Malaysia* 2010; 65: 138–142.
7. Marie I, Hatron PY, Levesque H, et al. Influence of age on characteristics of polymyositis and dermatomyositis in adults. *Medicine (Baltimore)* 1999; 78: 139–147.
8. Hill CL, Zhang Y, Sigurgeirsson B, et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. *Lancet* 2001; 357: 96–100.
9. Stockton D, Doherty VR and Brewster DH. Risk of cancer in patients with dermatomyositis or polymyositis, and follow-up implications: a Scottish population-based cohort study. *Br J Cancer* 2001; 85: 41–45.
10. Tiniakou E and Mammen AL. Idiopathic inflammatory myopathies and malignancy: a comprehensive review. *Clin Rev Allergy Immunol* 2017; 52: 20–33.
11. Teh CL, Wong JS and Soo HH. Polymyositis and dermatomyositis in Sarawak: a profile of patients treated in the Sarawak General Hospital. *Rheumatol Int* 2012; 32: 265–268.
12. Muñoz MA, Conejo-Mir JS, Congregado-Loscertales M, et al. The utility of positron emission tomography to find an occult neoplasm in a patient with dermatomyositis. *J Eur Acad Dermatol Venereol* 2007; 21: 1418–1419.
13. Selva-O'Callaghan A, Grau JM, Gámez-Cenzano C, et al. Conventional cancer screening versus PET/CT in dermatomyositis/polymyositis. *Am J Med* 2010; 123: 558–562.
14. Amoura Z, Duhaut P, Huong DL, et al. Tumor antigen markers for the detection of solid cancers in inflammatory myopathies. *Cancer Epidemiol Biomarkers Prev* 2005; 14: 1279–1282.
15. András C, Ponyi A, Constantin T, et al. Dermatomyositis and polymyositis associated with malignancy: a 21-year retrospective study. *J Rheumatol* 2008; 35: 438–444.
16. Bodoki L, Nagy-Vincze M, Griger Z, et al. Four dermatomyositis-specific autoantibodies-anti-TIF1γ, anti-NXP2, anti-SAE and anti-MDA5-in adult and juvenile patients with idiopathic inflammatory myopathies in a Hungarian cohort. *Autoimmun Rev* 2014; 13: 1211–1219.
17. Ichimura Y, Matsushita T, Hamaguchi Y, et al. Anti-NXP2 autoantibodies in adult patients with idiopathic inflammatory myopathies: possible association with malignancy. *Ann Rheum Dis* 2012; 71: 710–713.
18. Yang H, Peng Q, Yin L, et al. Identification of multiple cancer-associated myositis-specific autoantibodies in idiopathic inflammatory myopathies: a large longitudinal cohort study. *Arthritis Res Ther* 2017; 19: 259.
19. Fathi M, Dastmalchi M, Rasmussen E, et al. Interstitial lung disease, a common manifestation of newly diagnosed polymyositis and dermatomyositis. *Ann Rheum Dis* 2004; 63: 297–301.
20. Fahim A, Crooks MG, Wilmot R, et al. Serum carcinoembryonic antigen correlates with severity of idiopathic pulmonary fibrosis. *Respirology* 2012; 17: 1247–1252.
21. Wong RC, Klingberg S and Wilson R. CA15-3 and cancer associated serum antigen assays are alternatives to the KL-6 assay for measuring serum MUC-1 levels in patients with interstitial lung disease associated with polymyositis/dermatomyositis. *J Rheumatol* 2002; 29: 2021–2022.
22. Okada M, Suzuki K, Nakanishi T, et al. Serum levels of KL-6 are positively correlated with those of CA15-3 in patients with interstitial pneumonia associated with collagen diseases. *Respirology* 2006; 11: 509–510.
23. Bohan A and Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975; 292: 344–347.
24. Huang YL, Chen YJ, Lin MW, et al. Malignancies associated with dermatomyositis and polymyositis in Taiwan: a nationwide population-based study. *Br J Dermatol* 2009; 161: 854–860.
25. Tseng CW, Chen YM, Lai KL, et al. Clinical correlation between anti-Mi-2 antibodies and polymyositis/dermatomyositis in Chinese patients. *Formos J Rheumatol* 2014; 28: 34–41.
26. Deyo RA, Cherkin DC and Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; 45: 613–619.

27. Raghu G, Chen SY, Yeh WS, et al. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001–11. *Lancet Respir Med* 2014; 2: 566–572.
28. Kang EH, Lee EB, Shin KC, et al. Interstitial lung disease in patients with polymyositis, dermatomyositis and amyopathic dermatomyositis. *Rheumatology* 2005; 44: 1282–1286.
29. Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *J Clin Oncol* 2006; 24: 5313–5327.
30. Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol* 2007; 25: 5287–5312.
31. Sturgeon CM, Duffy MJ, Stenman UH, et al. National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers. *Clin Chem* 2008; 54: e11–e79.
32. Bruix J and Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; 53: 1020–1022.
33. Omata M, Lesmana LA, Tateishi R, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. *Hepatol Int* 2010; 4: 439–474.
34. O'Gradaigh D and Merry P. Tumour markers in dermatomyositis: useful or useless? *Br J Rheumatol* 1998; 37: 914.
35. Whitmore SE, Anhalt GJ, Provost TT, et al. Serum CA-125 screening for ovarian cancer in patients with dermatomyositis. *Gynecol Oncol* 1997; 65: 241–244.
36. Baldus SE, Engelmann K and Hanisch FG. MUC1 and the MUCs: a family of human mucins with impact in cancer biology. *Crit Rev Clin Lab Sci* 2004; 41: 189–231.
37. Kruit A, Gerritsen WB, Pot N, et al. CA 15-3 as an alternative marker for KL-6 in fibrotic lung diseases. *Sarcoidosis Vasc Diffuse Lung Dis* 2010; 27: 138–146.
38. Kim HR, Lee CH, Kim YW, et al. Increased CA 19-9 level in patients without malignant disease. *Clin Chem Lab Med* 2009; 47: 750–754.
39. Hsu C, Shen YC, Cheng CC, et al. Difference in the incidence trend of nasopharyngeal and oropharyngeal carcinomas in Taiwan: implication from age-period-cohort analysis. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 856–861.
40. Shen YC, Chang CJ, Hsu C, et al. Significant difference in the trends of female breast cancer incidence between Taiwanese and Caucasian Americans: implications from age-period-cohort analysis. *Cancer Epidemiol Biomarkers Prev* 2005; 14: 1986–1990.