

Characteristics of anti-transcriptional intermediary factor 1 gamma autoantibody-positive dermatomyositis patients in Singapore

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ABSTRACT

Introduction: This study aimed to determine the clinical profile and outcome of anti-transcriptional intermediary factor 1 gamma autoantibody (anti-TIF1- γ Ab)-positive dermatomyositis patients and propose cancer screening programmes based on regional cancer trends.

Method: Data on history, physical findings and investigations were collected using chart review on dermatomyositis patients seen at a tertiary hospital in Singapore from 1 January 2015 to 30 June 2021. Comparisons were made between anti-TIF1- γ Ab-positive and anti-TIF1- γ Ab-negative dermatomyositis.

Results: Ninety-six dermatomyositis patients were analysed and 36 patients were positive for anti-TIF1- γ Ab. Anti-TIF1- γ Ab-positive patients had more frequent heliotrope rashes, shawl sign, periungual erythema, holster sign, Gottron's papules, dysphagia and truncal weakness ($P<0.05$). They had less frequent interstitial lung disease, polyarthritis, cutaneous ulcers, palmar papules and mechanic's hands ($P<0.05$). After 48 months of follow-up, a higher proportion of anti-TIF1- γ Ab-positive patients developed cancer compared with Ab-negative patients (63.9% versus 8.5%; odds ratio 19.1, 95% confidence interval 6.1–59.8; $P<0.001$). Nasopharyngeal carcinoma (NPC) and breast cancer were the most common malignancies, followed by bowel, lung and non-Hodgkin lymphoma. Most malignancies (78.3%) occurred within 13 months prior to, or 4 months after the onset of dermatomyositis. The mortality rate for anti-TIF1- γ Ab-positive patients was significantly higher than Ab-negative patients (36.1% vs 16.7%, $P=0.031$), and Kaplan-Meier survival estimates at 24 months were 66% and 89%, respectively ($P=0.0153$).

Conclusion: These observational data support periodic screening of NPC and other malignancies in patients with anti-TIF1- γ Ab-positive dermatomyositis in Singapore.

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INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of acquired, systemic autoimmune conditions characterised by muscular and extramuscular manifestations. As a subset within the family of IIM, dermatomyositis is distinguished by cutaneous features and has twice the risk of associated malignancy than polymyositis.¹⁻³

Various meta-analyses have shown that between 10% and 47% of dermatomyositis patients have an underlying malignancy, and the associated cancers vary with

different geographical populations.¹⁻³ Ovarian, lung, pancreatic, non-Hodgkin lymphoma, stomach, colorectal and breast cancers are more frequently reported in Western studies.¹⁻³ In comparison, nasopharyngeal carcinoma (NPC) is more frequently reported among cancer-associated myositis (CAM) patients in studies from Taiwan, Hong Kong, Japan and South Korea, with a frequency of up to 40%.³⁻⁹

The discovery of myositis-specific autoantibodies (MSAs) associated with distinct clinical phenotypes is a major advancement that enables the identification of

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CLINICAL IMPACT

What is New

- Anti-transcriptional intermediary factor 1 gamma autoantibody (anti-TIF1- γ Ab) was the most common myositis-specific autoantibody subtype seen in our dermatomyositis patients.
- Nasopharyngeal carcinoma and breast cancers were the most common malignancies observed in our autoantibody-positive cohort.

Clinical Implications

- Periodic malignancy screening should be performed for patients with dermatomyositis, particularly those who are anti-TIF1- γ Ab-positive.
- Nasopharyngeal carcinoma screening should be included in the cancer surveillance programme for dermatomyositis patients in Singapore.

distinct patterns of disease. Among the MSAs, anti-transcriptional intermediary factor 1 gamma autoantibody (anti-TIF1- γ Ab) is strongly associated with malignancies in adult-onset dermatomyositis.^{10–14} Human TIF1- γ belongs to the tripartite motif (TRIM) containing protein and is involved in a broad range of biological processes and diverse pathological conditions, such as developmental disorders, neurodegenerative diseases, viral infections and cancer. It is found at varying levels in skeletal muscles and skin,^{15–17} and its involvement in the transforming growth factor TGF- β signalling pathway has been most extensively studied.^{18–20} TIF1- γ normally inhibits tumourigenesis by inhibiting TGF- β -induced epithelial-to-mesenchymal transition via mono-ubiquitination of *SMAD4* (a tumour suppressor gene). Both suppression and overexpression of TIF1- γ have been associated with different cancers depending on the cellular context and cancer stage.^{21–26} Inactivation, mutation or down-regulation of TIF1- γ by hypermethylation, histone modification, short non-coding microRNA or sumoylation can promote tumourigenesis, which has been reported in hepatocellular carcinoma, non-small-cell lung carcinoma and clear cell renal cell carcinoma.^{21,22} Overexpression of TIF1- γ has been described in early-stage breast cancer, and both early and advanced stage colorectal cancer.^{25,26}

In anti-TIF1- γ Ab-positive CAM, it is hypothesised that TIF1- γ functions as a tumour autoantigen and

triggers dermatomyositis through activation of both adaptive and innate immune responses.^{27–29} CAM has been reported to occur within 3 years prior to or following the onset of dermatomyositis, with the presence of anti-TIF1- γ Ab conferring a 9.37-fold higher risk of developing cancer with a 52% sensitivity and 92% specificity.^{10–14,30} Some of the characteristics observed in anti-TIF1- γ Ab-positive CAM patients include (1) a higher risk of developing cancer among those who are ≥ 39 years of age at the onset of dermatomyositis;^{14,31} (2) a higher prevalence of solid cancers compared to haematological cancers (19.9% versus 1.4%);^{2,30} and (3) increased risk of ovarian cancer in females.^{2,14,32} These observations were drawn mainly from studies on Western cohorts with a paucity of data from the Asian population, in particular, Southeast Asia.

Given the strong association between anti-TIF1- γ Ab and cancer, close surveillance for cancer in this subgroup of dermatomyositis patients to allow early detection and treatment is advocated. The International Myositis Assessment and Clinical Studies Group has established a special interest group that aims to develop evidence-based cancer screening guidelines for newly diagnosed IIM patients.³³ In addition, small studies have shown potential biomarker value in anti-TIF1- γ Ab titre serial measurements to monitor dermatomyositis activity for detecting cancer recurrence.³⁴

The objective of this study was to determine the clinical profile and outcomes of patients with anti-TIF1- γ Ab-positive dermatomyositis at a single tertiary centre in Singapore and to propose a cancer screening programme for Singapore dermatomyositis patients.

METHOD

We analysed dermatomyositis patients seen at the Department of Rheumatology, Allergy and Immunology in Tan Tock Seng Hospital, Singapore from 1 January 2015 to 30 June 2021. Inclusion criteria included age of onset ≥ 18 years and the diagnosis of either definite or probable IIM according to the Bohan and Peter criteria. The International Myositis Classification Criteria score was also calculated for each case and only those with a score of at least 55% (“probable IIM”) and cutaneous manifestations consistent with dermatomyositis were included.

Clinical information on disease manifestations, laboratory data, imaging data, presence of malignancy, treatment and outcome was obtained from medical chart review. The following parameters were assessed: age of onset, sex, clinical features, laboratory data at the time of dermatomyositis diagnosis, history of malignancy (including type, timing of diagnosis in relation to

dermatomyositis, staging and pathological classification), treatment for both dermatomyositis and malignancy, mortality rate, and cause of mortality. All patients were tested for the presence of MSA/myositis-associated autoantibodies (MAAs). Whole-blood samples were drawn into ethylenediaminetetraacetic acid (EDTA) tubes to enable separation of plasma by centrifugation, permitting autoantibody testing for determination of the presence of MSAs and MAAs using the Euroline Autoimmune Inflammatory Myopathies 16 Antigen Profile panel. All patients were followed up until mortality, loss to follow-up or 30 June 2021.

Ethics approval was granted. As strict local Personal Data Protection Act guidelines were observed and data collected would facilitate improvement in future patient care, waiver of patient consent was granted by the ethics committee.

Statistical analysis

Between-group comparisons of normally distributed measurement data were conducted using Student's *t*-test or the Mann-Whitney *U* test. The chi-square test was used to analyse differences between baseline characteristics data. To identify independent risk factors, the odds ratio (OR) and 95% confidence interval (CI) were analysed using multivariate Cox proportional hazards regression analysis. Variables with $P < 0.05$ in univariate analysis were analysed using the Kaplan-Meier curve and the log-rank test. All statistical analyses were carried out using Stata version 14.0 (StataCorp, College Station, US). The results were reported as the median (interquartile range [IQR]). $P < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

Demographic data

Of the 96 patients with dermatomyositis, 63 (65.6%) were women and 33 (34.4%) were men. The median age of the patients at the time of dermatomyositis onset was 57 years (IQR 44.75–64.00 years) and the median follow-up duration was 48 months (16.75–78.97 months). Patients were divided into 2 groups: 36 patients with anti-TIF1- γ Ab, and 60 without anti-TIF1- γ Ab. The most common MSA/MAAs detected in the anti-TIF1- γ Ab group were anti-Ro52 (37/60, 61.7%), anti-MDA5 (22/60, 36.7%) and anti-PL7 (13/60, 21.7%). Anti-NXP2 was found in 3 out of 96 dermatomyositis patients (3.1%), of which 1 co-existed in a patient with positive anti-TIF1- γ Ab. The proportion of patients with malignancy in the anti-TIF1- γ Ab-positive group was

significantly higher than in those without anti-TIF1- γ Ab. Demographic characteristics of the 2 groups are presented in Table 1.

Clinical data of patients with positive anti-TIF1- γ Ab

Of the 36 anti-TIF1- γ Ab-positive dermatomyositis patients, 10 (27.8%) were men and 26 (72.2%) were women. Six (16.7%) of this group were smokers and the median age of dermatomyositis diagnosis was 61.5 years (IQR 29–96). Twenty-three (63.9%) patients were diagnosed with malignancies; NPC and breast cancer were the most common with 6 (26.1%) patients each. Other malignancies included 2 gastrointestinal (13.0%), 2 lung (8.7%), 2 non-Hodgkin lymphoma (8.7%), and 1 (4.3%) each for cervical, fallopian tube, thyroid and kidney. Breast cancer (6/17, 35.3%), NPC (3/17, 17.6%) and gastrointestinal (2/17, 11.8%) were the most common types of malignancy in female CAM patients. NPC (3/6, 50%), followed by lung, gastrointestinal and non-Hodgkin lymphoma (1/6 for each, 16.7%) were most common in male CAM patients. Of those anti-TIF1- γ Ab-positive NPC, 66.6% presented with advanced stage (Stage III or more) and all had undifferentiated histology.

Cancer characteristics of those with and without anti-TIF1- γ Ab are presented in Table 2. Malignancy was detected at the time of dermatomyositis diagnosis in 7/23 (30.4%) patients, following dermatomyositis diagnosis in 7/23 (30.4%) patients, and prior to dermatomyositis diagnosis in 9/23 (39.2%) patients. Malignancy was detected within 1 year before or after dermatomyositis diagnosis in 17 patients (73.9%). Of the 23 cancer patients, 21 were diagnosed with both dermatomyositis and cancer at age 39 years and above. The remaining 2 were females diagnosed with dermatomyositis at age 29 and 32 years, respectively. Both had breast cancers diagnosed 13 months before and 20 months after dermatomyositis diagnosis, respectively. The former had a strong family history of cancer (breast and cervical) but the latter had none. Table 3 summarises the clinical information of the anti-TIF1- γ Ab-positive dermatomyositis patients with cancers.

Baseline and follow-up cancer screening

Our dermatomyositis patients underwent various combinations of cancer screening investigations. Investigations performed were based on patients' symptoms and signs, family cancer history, contraindications and patients' preferences. A total of 32 of the 96 dermatomyositis patients (33.3%) underwent a complete

Table 1. Demographic and clinical characteristics of patients with anti-TIF1- γ Ab-positive and anti-TIF1- γ Ab-negative dermatomyositis

N=96	Anti-TIF1- γ Ab-positive (n=36, 37.5%)	Anti-TIF1- γ Ab-negative (n=60, 62.5%)	P value
Demographics			
Age, median (range), years	61.5 (29–96)	54 (20–76)	0.005
Time from symptoms onset to diagnosis, median (range), months	2.5 (1–24)	3 (1–120)	0.137
Female, n (%)	26 (72.2)	37 (61.7)	0.292
Smoker, n (%)	6 (16.7)	9 (15.3)	0.855
Ethnicity, n (%)			0.352
Chinese	31 (86.1)	42 (70)	
Malay	5 (13.9)	12 (20)	
Indian	0	4 (6.7)	
Cutaneous manifestations			
Heliotrope rash	26 (72.2)	18 (30)	<0.001
Shawl sign	18 (50.0)	4 (6.7)	<0.001
Periungual erythema	25 (69.4)	20 (33.3)	0.001
Holster sign	8 (22.2)	2 (3.3)	0.005
Gottron's papules	26 (72.2)	27 (45.0)	0.009
Cutaneous ulcers	2 (5.6)	18 (30)	0.004
Mechanic's hands	4 (11.1)	20 (33.3)	0.015
Palmar papules	0	8 (13.3)	0.023
Violaceous rash	7 (19.4)	20 (33.3)	0.143
Inverse Gottron's	2 (5.6)	6 (10.0)	0.706
Musculoskeletal			
Proximal muscle weakness, n (%)	29 (80.6)	38 (63.3)	0.075
Amyopathy, n (%)	7 (19.4)	22 (36.7)	0.075
- Raised creatinine kinase >250 U/L, n (%)	1 (14.3)	11 (50.0)	-
- Abnormal electromyogram, n (%)	5 (71.4)	8 (36.3)	-
- Raised creatine kinase and abnormal electromyogram, n (%)	1 (14.3)	3 (13.6)	-
Truncal weakness, n (%)	10 (27.8)	6 (10.0)	0.024
Dysphagia, n (%)	15 (41.7)	9 (15.0)	0.003
Polyarthritis, n (%)	0	20 (33.3)	<0.001
Highest creatine kinase, median (range), U/L	473 (58–9512)	499.5 (35–36776)	0.54
Pulmonary			
Interstitial lung disease, n (%)	2 (5.6)	34 (56.7)	<0.001
Cancer and mortality			
Cancer, n (%)	23 (63.9) ^a	5 (8.5)	<0.001
Mortality, n (%)	13 (36.1)	10 (16.7)	0.031
Time from diagnosis to death (among those who died), median (range), months	12 (2–34)	4.5 (0–168)	0.419

^a Cancer data for one anti-TIF1- γ Ab-positive patient were not available

Table 2. Characteristics of anti-TIF1- γ Ab-positive and anti-TIF1- γ Ab-negative dermatomyositis patients with cancer

N=28	Anti-TIF1- γ Ab-positive (n=23)	Anti-TIF1- γ Ab-negative (n=5)
Demographics		
Age on dermatomyositis onset, median (range), years	64 (29–96)	52 (41–76)
Time from dermatomyositis diagnosis to cancer diagnosis, median (range), months	0 (-288–22)	2 (0–72)
Interquartile range for time from dermatomyositis diagnosis to cancer diagnosis in months	0–2	-8.5–2
Female, n (%)	17 (73.9)	1 (20)
Smoker, n (%)	4 (17.4)	1 (20)
Ethnicity, n (%)		
Chinese	21	4
Malay	2	1
Indian	-	-
Mortality, n (%)	10 (43.5)	2 (40)
Time from dermatomyositis diagnosis to death (among those who died), median (range), months	14 (5–34)	45 (16–73)
Cancer characteristics		
	Male	Female
Site		
Nasopharyngeal	3	3
Breast	-	6
Bowel	1	2
Lung	1	1
Thyroid	-	1
Cervical	-	1
Fallopian tube	-	1
Non-Hodgkin lymphoma	1	1
Kidney	-	1
Prostate	-	-
Tonsil	-	-
Advanced stage	13	3

baseline cancer screening comprising: (1) a neck and posterior nasal space (PNS) assessment with computed tomography (CT) scan of neck, magnetic resonance imaging (MRI) of the neck and PNS (MRI neck/PNS), and/or otolaryngology (ENT) review; (2) CT scan of the thorax/abdomen-pelvis (CT thorax/abdomen-pelvis); (3) oesophago-gastro-duodenoscopy (OGD); and (4) colonoscopy (or CT colonography). A higher proportion of anti-TIF1- γ Ab-positive patients (16/36, 44.4%) underwent a complete baseline cancer screen compared to the Ab-negative group (16/60, 26.7%). Seventy-five (78.1%) patients underwent at least a CT thorax/abdomen-pelvis scan as baseline cancer screen at dermatomyositis diagnosis. Of 63 female dermatomyositis patients, 34 (54%) underwent a baseline mammogram (MMG) and 7 (11.1%) received a Papanicolaou (Pap) smear. A higher proportion of anti-TIF1- γ Ab-positive female patients underwent MMG and Pap smear (MMG: 17/26, 65.4%; Pap smear: 6/26, 23.1%) compared to Ab negative group (MMG: 17/37, 45.9%; Pap smear: 1/37, 2.7%).

Clinical features associated with anti-TIF1- γ Ab-positive dermatomyositis

Clinical features found more commonly in anti-TIF1- γ Ab-positive compared to Ab-negative dermatomyositis patients were heliotrope rash (72.2% vs 30.0%, $P<0.001$), shawl sign (50.0% vs 6.7%, $P<0.001$), periungual erythema (69.4% vs 33.3%, $P=0.001$), holster sign (22.2% vs 3.3%, $P=0.005$), Gottron's papules (72.2% vs 45.0%, $P=0.009$), dysphagia (41.7% vs 15.0%, $P=0.003$), truncal weakness (27.8% vs 10.0%, $P=0.024$) and proximal myopathy (80.6% vs 63.3%, $P=0.075$). Patients with raised creatine kinase >250 U/L in both groups were similar: 24/36 (66.7%) in the anti-TIF1- γ Ab-positive group and 38/60 (63.3%) in Ab-negative patients. Presence of interstitial lung disease (5.6% vs 56.7%, $P<0.001$), polyarthritis (0% vs 33.3%, $P<0.001$), cutaneous ulcers (5.6% vs 30.0%, $P=0.004$), palmar papules (0% vs 13.3%, $P=0.023$) and mechanic's hands (11.1% vs 33.3%, $P=0.015$) were less common in the Ab-positive group (Table 1).

Immunosuppressive treatment of anti-TIF1- γ Ab-positive CAM patients

The majority (18/23, 78.3%) of our anti-TIF1- γ Ab-positive CAM patients displayed significant signs and symptoms that required initial high-dose corticosteroid treatment in the forms of intravenous hydrocortisone and/or pulsed methylprednisolone.

Table 3. Summary of anti-TIF1- γ Ab-positive dermatomyositis patients with cancer

Case	Age at diagnosis of dermatomyositis (years)	Sex	Ethnicity	Cancer and treatment		Time from dermatomyositis diagnosis to cancer diagnosis (months)	Dermatomyositis treatment	Outcome of dermatomyositis/ outcome of cancer/cause of death (if applicable)
				Site/Type	Stage			
1	29	Female	Malay	Breast/metastatic carcinoma (ER+/PR-/HER2+)	IIIA	-13	MP, hydrocort, pred, HCQ, AZA, MTX, MMF, IVIg	Relapse/ remission/ -
2	32	Female	Chinese	Breast/invasive ductal (ER/PR/HER2 not available)	IIA	20	MP, hydrocort, pred, AZA, MTX, CsA, IVIg	Improved and stable/ remission/ -
3	47	Female	Chinese	Nasopharyngeal/ undifferentiated	III	1	MP, hydrocort, pred, HCQ, AZA, MTX, CsA, IVIg	Improved and stable/ remission/ -
4	49	Female	Chinese	Nasopharyngeal/ undifferentiated	II	0	Pred, AZA, MTX	Improved and stable/ remission/ -
5	52	Female	Chinese	Bowel/adenocarcinoma	IIIB	0	Pred, HCQ, AZA	Improved and stable/ remission / -
6	55	Female	Chinese	Breast/invasive ductal (ER-/PR-/HER2+)	IIIA	4	Hydrocort, pred, HCQ, IVIg	Improved and stable/ remission/ -
7	57	Female	Chinese	Breast/invasive ductal (ER-/PR-/HER2 equivocal)	IIA	0	Pred, HCQ	Improved and stable/ remission/ -
8	63	Female	Chinese	Breast/invasive ductal (ER-/PR-/HER2 equivocal)	IIA	3	Pred, HCQ	Improved and stable/ remission/ -
9	65	Female	Chinese	Thyroid/follicular carcinoma	I	4	MP, hydrocort, pred, HCQ, MTX, CsA, IVIg	Improved and stable/ remission/ -
10*	73	Female	Chinese	Renal/transitional cell carcinoma	IV	-12	MP, hydrocort, pred	Improved and stable/ - / -
11	76	Female	Chinese	Breast/papillary cell carcinoma (ER+/PR+/HER2 equivocal)	IIA	3	Hydrocort, pred, HCQ, AZA, IVIg	Improved and stable/ remission/ -
12	63	Male	Chinese	Nasopharyngeal/ undifferentiated	III	0	MP, hydrocort, pred, HCQ, IVIg	Improved and stable/ remission/ -
13	64	Male	Chinese	Nasopharyngeal/ undifferentiated	I	0	Pred, MTX	Improved and stable/ remission/ -
14	64	Female	Chinese	Fallopian tube/poorly differentiated	IIIA	-4	Hydrocort, pred, IVIg	Improved and stable/ metastatic/died, no available information

Table 3. Summary of anti-TIF1- γ Ab-positive dermatomyositis patients with cancer (Cont'd)

Case	Age at diagnosis of dermatomyositis (years)	Sex	Ethnicity	Cancer and treatment		Time from dermatomyositis diagnosis to cancer diagnosis (months)	Dermatomyositis treatment	Outcome of dermatomyositis/ outcome of cancer/cause of death (if applicable)
				Site/Type	Stage			
15	67	Female	Chinese	Nasopharyngeal/undifferentiated	IVB	Chemotherapy	MP, hydrocort, pred, AZA, MTX, IVIg	Persistently active/metastatic/died, nasopharyngeal carcinoma
16	68	Female	Chinese	Bowel/adenocarcinoma	IIIC	Chemotherapy, radiotherapy	MP, hydrocort, IVIg	Active/metastatic/died, pneumonia
17	77	Female	Chinese	Non-Hodgkin lymphoma/diffuse large B-cell lymphoma	IVA	Chemotherapy	Hydrocort	Active/care transferred, no available information/died, no available information
18	80	Female	Malay	Lung/adenocarcinoma (EGFR exon21 L858R)	IV	Chemotherapy, tyrosine kinase inhibitor	Hydrocort, pred, HCQ, AZA	Persistently active/metastatic/died, no available information
19	96	Female	Chinese	Cervical	II	Radiotherapy	Hydrocort, pred, HCQ	Improved and stable/metastatic/died, myocardial infarction and infection
20	42	Male	Chinese	Nasopharyngeal/undifferentiated	IVB	Surgery, chemotherapy, radiotherapy	MP, hydrocort, pred, HCQ, AZA, CsA, IVIg	Persistently active/metastatic/died, nasopharyngeal carcinoma
21	74	Male	Chinese	Non-Hodgkin lymphoma/zone lymphoma, MALT	I	Surgery	MP, hydrocort, pred, HCQ, AZA, MMF, IVIg	Improved and stable/remission/died, intracerebral haemorrhage
22	77	Male	Chinese	Lung/non-small cell lung carcinoma	IIIA	Chemotherapy	Hydrocort, pred	Persistently active/metastatic/died, pneumonia
23 ^b	89	Male	Chinese	Bowel	IV	Surgery	MP, hydrocort, pred, IVIg	Active/relapse/died, colorectal cancer

AZA: azathioprine; CsA: ciclosporin; EGFR: epidermal growth factor receptor; HCQ: hydroxychloroquine; hydrocort: hydrocortisone; IVIg: intravenous immunoglobulin; MALT: mucosa-associated lymphoid tissue; MMF: mycophenolate mofetil; MP: methylprednisolone; MTX: methotrexate; pred: prednisolone

^a Patient returned to the neighbouring home country after initial management at our centre.

^b Patient was first diagnosed with ascending colon carcinoma 288 months prior to dermatomyositis diagnosis and underwent hemicolectomy with adjuvant chemotherapy. Interval surveillance did not reveal cancer recurrence. Presumptive recurrence of metastatic cancer at diagnosis of dermatomyositis with mass at the gastroesophageal junction and metastatic lesions to liver and lung; patient declined scopes and biopsy.

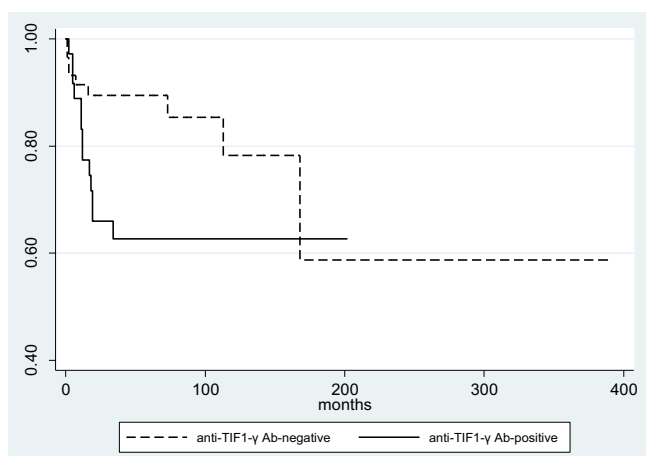


Fig. 1. Kaplan-Meier survival estimates for patients with anti-transcriptional intermediary factor 1 gamma autoantibody (anti-TIF1- γ Ab)-positive and anti-TIF1- γ Ab-negative dermatomyositis.

Thirteen patients (56.5%) received intravenous immunoglobulins (IVIg) as a corticosteroid-sparing agent for treating dermatomyositis while receiving concurrent cancer-treatment therapies. Among these 13 patients, 6 improved and remained stable, 1 improved but sustained a relapse of dermatomyositis, and 6 died. Of the latter 6, 5 had advanced cancers of at least stage III or worse. Other immunomodulators used in our patients were hydroxychloroquine (13), azathioprine (10), methotrexate (7), ciclosporin (4), and mycophenolate mofetil (2). More CAM survivors (8/13, 61.5%) received immunomodulators compared to those who died (4/10, 40.0%).

Survival analysis

A total of 23 mortalities occurred among the 96 dermatomyositis patients (24.0%) during the follow-up period. The mortality rate was significantly higher in anti-TIF1- γ Ab-positive ($n=13$, 36.1%) compared to the Ab-negative group ($n=10$, 16.7%, $P=0.031$). Within the anti-TIF1- γ Ab-positive group, mortality was higher in those patients with malignancy ($n=10$, 76.9%) than those without ($n=3$, 23.1%). Among the CAM mortalities, 8/10 (80.0%) had advanced cancers of at least stage III or worse. Kaplan-Meier survival curves (Fig. 1) revealed a significant difference in survival times between both groups, with 24-month survival in the anti-TIF1- γ Ab-positive group at 66%, and 89% in the anti-TIF1- γ Ab-negative group (log-rank test $P=0.0153$).

DISCUSSION

To our knowledge, this is the first study that describes the clinical profile and outcomes of patients with anti-TIF1- γ Ab-positive dermatomyositis in a multiethnic Southeast Asian cohort. Our results revealed a significantly higher prevalence of malignancy among

anti-TIF1- γ Ab-positive dermatomyositis patients compared to Ab-negative ones (63.9 vs 8.3%) with a diagnostic odds ratio (DOR) of 19.1 (95% CI 6.1–59.8; $P<0.001$). This is consistent with the reported overall DOR of 9.37 (95% CI 5.37–16.34) among anti-TIF1- γ Ab-positive IIM patients in a meta-analysis performed by Best et al.³⁰ The sensitivity and specificity of anti-TIF1- γ Ab for CAM diagnosis in our study were 82.14% and 80.88%, respectively, indicating its value in predicting CAM. The median time interval between cancer and dermatomyositis diagnosis in the Ab-positive patients was 0 month, with interquartile range of 8.5 months before and 2 months after dermatomyositis diagnosis. Eighteen CAM patients (78.3%) had cancer in the period of 13 months before and 4 months after dermatomyositis diagnosis. Our study, therefore, agrees with the observation that cancers were more likely to be diagnosed during the year before and after myositis onset, with a progressive decrease thereafter that has been reported in other studies.¹

In terms of clinical features, the presence of cutaneous manifestations like heliotrope rash, shawl sign, periungual erythema, holster sign, and Gottron's papules, as well as dysphagia were significantly more common in our anti-TIF1- γ Ab-positive group compared with the Ab-negative group. On the other hand, the findings of interstitial lung disease and polyarthritides were significantly uncommon. These clinical features are congruent with other reports and would be useful in describing the anti-TIF1- γ Ab-positive dermatomyositis phenotype in places where testing of MSA/MAAs is not readily accessible.¹

Contrary to the observations made by Oldroyd et al. and Fujimoto et al., where no patients with anti-TIF1- γ Ab-positive CAM developed cancer below age 39 years, 2 of our patients developed cancer below this age. Our findings indicate the need to exercise high vigilance in cancer screening among anti-TIF1- γ Ab-positive dermatomyositis patients regardless of age, particularly those with a family history of cancer.^{14,31}

In terms of cancer types, almost all CAM patients suffered from solid organ cancers (26/28, 92.9%) vs haematological malignancy (2/28, 7.1%). These findings were consistent with the observations made by Best et al. in a meta-analysis of 18 studies on adult dermatomyositis patients, which found a higher prevalence of solid organ cancers (19.9%) compared with haematological malignancies (1.4%).³⁰ Among all anti-TIF1- γ Ab-positive dermatomyositis patients, NPC and breast cancer were the most prevalent malignancies (each 6/23, 26.1%); NPC was the most common cancer among males (3/6, 50%) and second-most common cancer

among the females (3/17, 17.6%). A similar observation on the high prevalence of NPC among Asian CAM patients was made in various studies before TIF1- γ was discovered and/or MSAs/MAAs were widely tested.⁴⁻⁹

Breast cancer was the most common cancer among anti-TIF1- γ Ab-positive dermatomyositis female patients (6/17, 35.3%) in our study, which was similar to a large UK-based adult dermatomyositis cohort study by Oldroyd et al.¹⁴ However, unlike the UK cohort, none of our patients had ovarian cancer.¹⁴ In a separate Scandinavian cohort study, ovarian cancer was the most common cancer followed by breast cancer in female dermatomyositis patients.² Breast cancer was not found to be the most common cancer among a Korean cohort, but ovarian cancers were reported among the same group of CAM patients.³² Overall, these findings indicate significant variability in the types of cancers found in CAM patients dependent on geographical location, and therefore cancer screening programmes need to take local disease patterns into account.

Given the strong association between dermatomyositis and malignancy, especially NPC, our centre has developed a specific cancer screening programme for newly diagnosed dermatomyositis patients. On diagnosis, patients undergo an MRI neck/PNS, CT thorax/abdomen-pelvis, an ENT review, OGD and colonoscopy. Females also undergo an MMG and Pap smear. In the higher cancer-risk anti-TIF1- γ Ab-positive group, more stringent cancer screening in the immediate 3 years after dermatomyositis diagnosis is offered. This programme includes a 4-monthly ENT review and yearly CT neck/thorax/abdomen-pelvis. Annual MMG and Pap smears are offered to females. The ENT review for NPC surveillance comprises (1) oral cavity examination, (2) endoscopy of the aero-digestive tract (nasal cavity, nasopharynx, oropharynx and hypopharynx), (3) examination for cervical lymph nodes, and (4) ear examination to look for middle ear effusion. For anti-TIF1- γ Ab-negative dermatomyositis patients, a 6-monthly otolaryngology review is offered, and the remaining imaging and Pap smear are repeated based on conventional age/sex-specific screening recommendations and initial surveillance results. The frequency of repeated endoscopy depends on findings from the initial assessments for all patients. Tumour markers are not mandated or used in isolation for cancer screening due to their low sensitivity in the early stages of malignancy.^{1,35}

IVIg with high-dose glucocorticoids was used at onset in most of our CAM patients. Commonly used immunosuppressants to induce remission in severe IIM patients, such as cyclophosphamide and mycophenolate

mofetil, were generally not used initially, avoided or delayed, as patients were often commenced on chemotherapy agents at the time of diagnosis. The evidence on the efficacy of IVIg for CAM remains sparse and is limited by the poor long-term patient outcome from concomitant malignancy, with very few case reports and small retrospective studies performed to date.³⁶⁻⁴⁰ Despite this, we feel that a reasonable approach is to treat CAM patients with prednisolone (1mg/kg/day) and/or IVIg. We note that Selva-O'Callaghan et al. recommend treating CAM patients with prednisolone, IVIg (2g/kg/month) and/or ciclosporin (3–5mg/kg/day), in view of the overall immunomodulatory vs immunosuppressive roles of these agents.¹ In addition, we work closely with oncologists and surgeons to coordinate therapeutic plans in order to optimise patients for surgery if required and avoid potential drug interactions between chemotherapy and immunosuppressive therapeutics.

Limitations included the retrospective nature of this study, which may lead to inaccuracies in the identification of the exact onset of dermatomyositis, resulting in under- or over-estimation of the temporal relationship between the onset of dermatomyositis and cancer occurrence. Further, our centre neither repeats MSA/MAA test following dermatomyositis/cancer treatment nor measures anti-TIF1- γ Ab titres routinely, and hence no conclusions can be drawn on using anti-TIF1- γ Ab titres as biomarkers.^{14,34}

CONCLUSION

This study confirms the strong association between anti-TIF1- γ Ab positivity and malignancy in dermatomyositis patients and the long-term temporal relationship between the onset of dermatomyositis and cancer in these patients. Most Ab-positive CAM patients developed cancers in the interval of 1 year before and 1 year after dermatomyositis-onset and are ≥ 39 years of age at the onset of dermatomyositis. There was a higher prevalence of solid cancers, and NPC and breast cancer were the most common malignancy in our study population. When managing dermatomyositis patients, we recommend additional attention on cancer screening be paid towards those who are anti-TIF1- γ Ab-positive, at the time of dermatomyositis diagnosis, and for at least the subsequent 3 years. Although older patients are at higher risk of developing cancers, younger anti-TIF1- γ Ab-positive patients are not spared the risk of malignancy and should also undergo routine screening. In terms of screening strategy, a customised approach based on local cancer trends should be taken.

Ethics

This study complies with the Declaration of Helsinki. Ethics approval was granted. Waiver of patient consent was also granted by the ethics committee as strict Singapore Personal Data Protection Act guidelines were observed and data collected would facilitate improvement in future patient care.

Data availability statement

The datasets generated and/or analysed during the current study are available from the corresponding author on request.

REFERENCES

- Selva-O'Callaghan A, Trallero-Araguas E, Pinal-Fernandez I. Cancer-associated myositis. In: Aggarwal R, Oddis CV (Eds). *Managing Myositis: A practical guide*. 1st Ed., 2020. Springer, Cham. 2020;25:237-45.
- 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.
- Yang Z, Lin F, Qin B, et al. Polymyositis/dermatomyositis and malignancy risk: a metaanalysis study. *J Rheumatol* 2015;42:282-91.
- Zhang W, Jiang SP, Huang L. Dermatomyositis and malignancy: a retrospective study of 115 cases. *Eur Rev Med Pharmacol Sci* 2009;13:77-80.
- Chen YJ, Wu CY, Huang YL, et al. Cancer risks of dermatomyositis and polymyositis: Nationwide cohort study in Taiwan. *Arthritis Res Ther* 2010;12:R70.
- Tang MM, Thevarajah S. Paraneoplastic dermatomyositis: a 12-year retrospective review in the department of dermatology Hospital Kuala Lumpur. *Med J Malaysia* 2010;65:138-42.
- Chan HL. Dermatomyositis and cancer in Singapore. *Int J Dermatol* 1985;27:447-50.
- Peng JC, Sheen TS, Hsu MM. Nasopharyngeal carcinoma with dermatomyositis: analysis of 12 cases. *Arch Otolaryngol Head Neck Surg* 1995;121:1298-301.
- Teoh JW, Yunus RM, Hassan F, et al. Nasopharyngeal carcinoma in dermatomyositis patients: a 10-year retrospective review in Hospital Selayang, Malaysia. *Rep Pract OncolRadiother* 2014;19:332-6.
- Targoff IN, Mamyrova G, Trieu EP, et al. A novel autoantibody to a 155-kd protein is associated with dermatomyositis. *Arthritis Rheum* 2006;54:3682-9.
- Chinoy H, Fertig N, Oddis CV, et al. The diagnostic utility of myositis autoantibody testing for predicting the risk of cancer-associated myositis. *Ann Rheum Dis* 2007;66:1345-9.
- Trallero-Araguás E, Rodrigo-Pendás JA, Selva-O'Callaghan A, et al. Usefulness of anti-p155 autoantibody for diagnosing cancer-associated dermatomyositis: a systematic and meta-analysis. *Arthritis Rheum* 2012;64:523-32.
- Kaji K, Fujimoto M, Hasegawa M, et al. Identification of a novel autoantibody reactive with 155 and 140 kDa nuclear proteins in patients with dermatomyositis: an association with malignancy. *Rheumatology (Oxford)* 2007;46:25-8.
- Oldroyd A, Sergeant JC, New P, et al. The temporal relationship between cancer and adult onset anti-transcriptional intermediary factor 1 antibody-positive dermatomyositis. *Rheumatology* 2019;58:650-5.
- Venturini L, You J, Stadler M, et al. TIF1gamma, a novel member of the transcriptional intermediary factor 1 family. *Oncogene* 1999;18:1209-17.
- Andrieux G, Fattet L, Le Borgne M, et al. Dynamic regulation of TGF- β signaling by TIF1 γ : a computational approach. *PLoS One* 2012;7:e33761.
- Hatakeyama S. TRIM proteins and cancer. *Nat Rev Cancer* 2011;11:792-804.
- Dupont S, Zaccagna L, Cordenonsi M, et al. Germ-layer specification and control of cell growth by Ectoderm, a Smad4 ubiquitin ligase. *Cell* 2005;121:87-99.
- He W, Dorn DC, Erdjument-Bromage H, et al. Hematopoiesis controlled by distinct TIF1 γ and Smad4 branches of the TGF β pathway. *Cell* 2006;125:929-41.
- Dupont S, Inui M, Newfeld SJ. Regulation of TGF- β signal transduction by mono- and deubiquitylation of Smads. *FEBS Lett* 2012;586:1913-20.
- Ding ZY, Jin GN, Wang W, et al. Reduced expression of transcriptional intermediary factor 1 γ promotes metastasis and indicates poor prognosis of hepatocellular carcinoma. *Hepatology* 2014;60:1620-36.
- Wang L, Yang H, Lei Z, et al. Repression of TIF1c by SOX2 promotes TGF- β -induced epithelial mesenchymal transition in non-small-cell lung cancer. *Oncogene* 2016;35:867-77.
- Vincent DF, Yan KP, Treilleux I, et al. Inactivation of TIF1 γ cooperates with Kras to induce cystic tumors of the pancreas. *PLoS Genet* 2009;5:e1000575.
- Vincent DF, Gout J, Chuvp N, et al. TIF1 γ suppresses murine pancreatic tumoral transformation by a Smad4-independent pathway. *Am J Pathol* 2012;180:2214-21.
- Kassem L, Deygas M, Fattet L, et al. TIF1 γ interferes with TGF β 1/SMAD4 signaling to promote poor outcome in operable breast cancer patients. *BMC Cancer* 2015;15:453.
- Jain S, Singhal S, Francis F, et al. Association of overexpression of TIF1 γ with colorectal carcinogenesis and advanced colorectal adenocarcinoma. *World J Gastroenterol* 2011;17:3994-4000.
- Scholtissek B, Ferring-Schmitt S, Maier J, et al. Expression of the autoantigen TRIM33/TIF1 γ in skin and muscle of patients with dermatomyositis is upregulated, together with markers of cellular stress. *Clin Exp Dermatol* 2017;42:659-62.
- Suber TL, Casciola-Rosen L, Rosen A. Mechanisms of disease: autoantigens as clues to the pathogenesis of myositis. *Nat Clin Pract Rheumatol* 2008;4:201-9.
- Fiorentino D, Casciola-Rosen L. Autoantibodies to transcription intermediary factor 1 in dermatomyositis shed insight into the cancer-myositis connection. *Arthritis Rheum* 2012;64:346-9.
- Best M, Molinari N, Chasset F, et al. Use of anti-transcriptional intermediary factor 1 gamma antibody in identifying adult dermatomyositis patients with cancer: a systematic review and meta-analysis. *Acta Derm Venereol* 2019;99:256-62.
- Fujimoto M, Hamaguchi Y, Kaji K, et al. Myositis-specific anti-155/140 autoantibodies target transcription intermediary factor 1 family proteins. *Arthritis Rheum* 2012;64:513-22.
- Kang EH, Lee SJ, Ascherman DP, et al. Temporal relationship between cancer and myositis identifies two distinctive subgroups of cancers: impact on cancer risk and survival in patients with myositis. *Rheumatology (Oxford)* 2016;55:1631-41.
- Oldroyd AGS, Allard AB, Callen JP, et al. A systematic review and meta-analysis to inform cancer screening guidelines in idiopathic inflammatory myopathies. *Rheumatology* 2021;60:2615-28.
- Shimizu K, Kobayashi T, Kano M, et al. Anti-transcriptional intermediary factor 1- γ antibody as a biomarker in patients with dermatomyositis. *J Dermatol* 2020;47:64-8.

35. Wong RC, Brown S, Clarke BE, et al. Transient elevation of the tumor markers CA 15-3 and CASA as markers of interstitial lung disease rather than underlying malignancy in dermatomyositis sine myositis. *J Clin Rheumatol* 2002;8:204-7.
 36. Hoa SAT, Hudson M. Critical review of the role of intravenous immunoglobulins in idiopathic inflammatory myopathies. *Semin Arthritis Rheum* 2017;46:488-508.
 37. Sampson JB, Smith SM, Smith AG, et al. Paraneoplastic myopathy: a response to intravenous immunoglobulin. *Neuromuscul Disord* 2007;17:404-8.
 38. Neri RS, Barsotti V, Iacopetti G, et al. Cancer-associated myositis: a 35-year retrospective study on a monocentric cohort. *Rheumatol Int* 2014;34:565-9.
 39. Aslanidis S, Pyrpasopoulou A, Kartali N, et al. Successful treatment of refractory rash in paraneoplastic rash in paraneoplastic amyopathic dermatomyositis. *Clin Rheumatol* 2007;26:1198-200.
 40. Kikuchi-Numagami K, Sato M, Tagami H. Successful treatment of a therapy-resistant severely pruritic skin eruption of malignancy-associated dermatomyositis with high dose intravenous immunoglobulin. *J Dermatol* 1996;23:340-3.
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