An extragonadal germ cell tumor with dermatomyositis: A case report and literature review

YU FUJIWARA[1], NAOKI FUKUDA[1], AKIHIRO OHMOTO[1], KENJI NAKANO[1], MAKIKO ONO[1], SHINICHIRO TAIRA[1], JUNICHI TORII[2], MANABU TAKAMATSU[3] and SHUNJI TAKAHASHI[1]

Departments of [1]Medical Oncology; [2]Head and Neck Oncology and [3]Pathology, The Cancer
Institute Hospital of Japanese Foundation for Cancer Research, Tokyo 1350063, Japan

Abstract. The risk of malignancy in inflammatory myopathy patients is well recognized. However, the incidence of germ cell tumor (GCT) with inflammatory myopathy is low, and most reported cases of GCT also exhibit testicular tumors. Therefore, a case of extragonadal GCT with dermatomyositis (DM) is reported in the current study to better understand this paraneoplastic syndrome. A 53-year-old man presented with bilateral cervical lymph node enlargement. A lymph node biopsy showed embryonal carcinoma, and computed tomography showed multiple lymph node and lung metastases. A period of one month after bleomycin, etoposide and cisplatin (BEP) chemotherapy, this patient developed an erythematous eruption over the extensor surfaces of bilateral fingers, or Gottron's sign and facial erythema. The patient was diagnosed with DM with a positive anti-TIF-1γ-antibody result. High-dose prednisolone was effective, and there has been no evidence of cancer recurrence for over one year. The literature review identified 17 cases of GCT with inflammatory myopathy that have been reported so far, and it was indicated that this is the first case of extragonadal GCT with DM following chemotherapy. This case highlights the importance of monitoring after the completion of cancer treatment, as distinctive dermal and muscular symptoms should cause us to consider the possibility of paraneoplastic inflammatory myopathy.

Correspondence to: Dr Naoki Fukuda, Department of Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 1350063, Japan
E-mail: naoki.fukuda@jfcr.or.jp

Introduction

Inflammatory myopathies, i.e., dermatomyositis (DM) and polymyositis (PM), are well recognized in association with malignancies. The first case of malignancy-associated inflammatory myopathy was described in 1916, which occurred with gastric cancer (1). Subsequently, ovarian cancer cases were reported in 1935 (2). Previous studies summarized the type of cancer with inflammatory myopathy. Ovarian, gastrointestinal, and lung cancers and lymphoma are relatively common, but germ cell tumors (GCTs) are rare (3-5). The typical clinical course of paraneoplastic inflammatory myopathy is that dermal and muscular symptoms precede the diagnosis of malignancy. In more than half of cases, the diagnosis of inflammatory myopathy precedes the diagnosis of malignancy (3,5). However, a case of extragonadal GCT with DM that occurred after completing chemotherapy for GCT is presented. On reviewing previous literature describing GCT with inflammatory myopathy, this is the first case of GCT whose primary site was extragonadal and the diagnosis of DM was made after the treatment for cancer. Moreover, its unique clinical course would be useful to inform oncologists that, even after treatment for the cancer itself, dermal and muscular symptoms such as facial erythema can be useful as signs for the diagnosis of paraneoplastic inflammatory myopathy.

Materials and methods

Information about this case was extracted from the medical records of The Cancer Institute Hospital of the Japanese Foundation for Cancer Research. For the literature review, the search terms to identify previous cases on PubMed were: 'Dermatomyositis, germ cell tumor'; 'dermatomyositis, testicular'; 'polymyositis, germ cell tumor'; and 'polymyositis, testicular'. Articles without abstracts or information about the clinical course were excluded. Articles written in languages other than English were also excluded.

Results

A 53-year-old man was referred to our hospital with suspected cancer of unknown origin. He complained of cervical lymph node enlargement and underwent contrast computed

Table I. Initial laboratory data.

A, Complete blood cell

Variable	Value	Unit
WBC	5,100	/μl
Stab+Seg	54.3	%
Lymphocyte	31.2	%
Monocyte	11.9	%
Eosinophil	1.5	%
Basophil	1.1	
RBC	477	10^4/μl
Hgb	15.9	g/dl
PLT	217,000	/μl

B, Biochemistry

TP	7.7	g/dl
Alb	4.5	g/dl
LDH	727	IU/l
T-Bil	0.8	mg/dl
AST	32	U/l
ALT	32	U/l
ALP	294	U/l
γGTP	50	U/
CK	65	U/Ll
BUN	12.0	mg/dl
Cr	0.84	mg/dl
eGFR	75.1	ml/min/l
Na	141	mEq/l
K	4.4	mEq/l
Cl	105	mEq/l
Ca	9.1	mg/dl
CRP	0.06	mg/dl

C, Infectious diseases

Variable	Value	Unit
HBs Ag	0.0	IU/ml
HBs Ab	0.45	mIU/ml
HCV Ab	Negative	
HIV Ab	Negative	

D, Tumor markers

Variable	Value	Unit
CEA	1.8	ng/ml
SCC	1.1	ng/ml
AFP	1.1	ng/ml
HCG	<1.0	mIU/ml
β-HCG	<0.1	ng/ml

E, Coagulation test

Variable	Value	Unit
PT	13.6	Second

Table I. Continued.

E, Coagulation test

Variable	Value	Unit
PT-INR	0.98	
APTT	33.2	Second
Fibrinogen	386	mg/dl
D-Dimer	0.38	μg/ml

WBC, white blood cell; RBC, red blood cell; Hgb, hemoglobin; PLT, platelet; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; SCC, squamous cell carcinoma; AFP, alpha fetoprotein; HCG, human chorionic gonadotropin; PT, prothrombin time; PT-INR, prothrombin time international normalized ratio; APTT, activated partial thromboplastin time; TP, total protein; Alb, albumin; LDH, lactate dehydrogenase; T-Bil, Total bilirubin; γGTP, gamma glutamyl transpeptidase; CK, creatine kinase; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; HBs Ag, hepatitis B surface antigen; HBs Ab, hepatitis B surface antibody; HCV Ab, hepatitis C antibody; HIV Ab, human immunodeficiency virus antibody.

tomography (CT), positron emission tomography (PET), and diagnostic cytology. Although poorly differentiated cancer was suspected on cytology, the primary site was not detected by imaging modalities. His past medical history included inguinal hernia and appendicitis in childhood, a ureterocele at age 15 years, fracture of the fibula at age 20 years, and ongoing hypertension and hyperuricemia. The patient's medications included amlodipine, valsartan, allopurinol, and diclofenac as needed. His father had prostate cancer at the age of 60 years. He drank alcohol every day, had no smoking history, and had not been exposed to toxins or illegal drugs. He worked as a bank clerk without any contacts with sick people. His vital signs were stable. On physical examination, cervical lymph nodes, 2x2 cm in size, were palpable bilaterally. Other examinations including chest, abdomen, genitals, extremities, and a neurological examination showed no abnormal findings. Laboratory data showed elevated lactate dehydrogenase (727 U/L, normal range: 124-222 U/L). The blood cell count was normal, and the chemistry panel showed no other abnormalities. α-fetoprotein (AFP) and human chorionic gonadotropin (HCG) were both under the lower limits (Table I). Contrast CT showed enlargement of bilateral cervical lymph nodes (35 mm x 29 mm), anterior mediastinal lymph nodes (49 mm x 30 mm), and para-aortic lymph nodes at the L2 vertebral level (25 mm x 18 mm) and multiple lung nodules, but no tumor in the testis (Fig. 1). Gastrointestinal and colorectal endoscopy found no evidence of malignancy. A needle biopsy was performed from a cervical lymph node twice. Histologically, the biopsy specimen showed proliferation of cancer cells forming a sheet-like structure with coagulative necrosis (Fig. 2A). The cancer cells showed enlarged oval nuclei with conspicuous nucleoli and pale cytoplasm (Fig. 2B). The differential diagnoses were squamous cell carcinoma, undifferentiated carcinoma and GCT, and immunohistochemistry showed that the cancer cells were positive for SALL4, OCT4, and CD30 (Fig. 3A-C). AFP, HCG
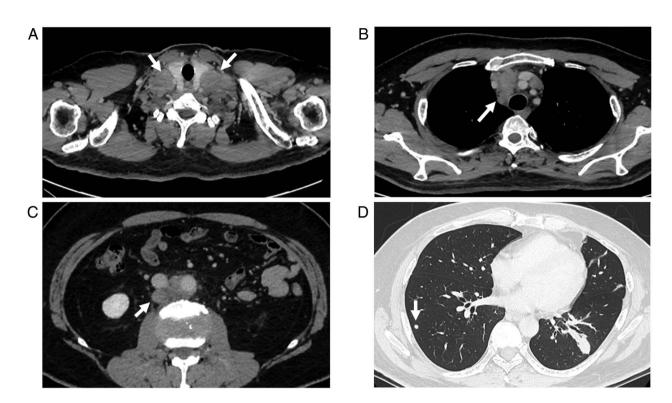
Figure 1. CT images at diagnosis of the germ cell tumor. (A) Enlarged bilateral cervical lymph nodes (arrow). (B) Enlarged bilateral mediastinal lymph nodes (arrow). (C) Enlarged paraaortic lymph nodes (arrow). (D) Lung metastases (arrow).
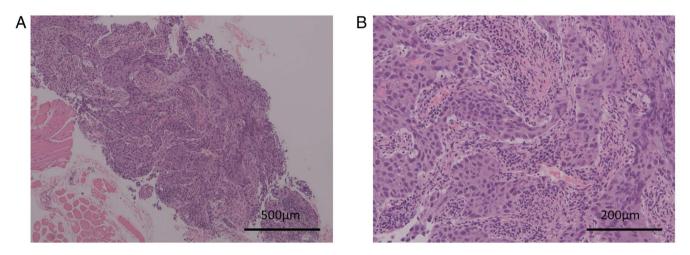

Figure 2. Pathological findings of cervical lymph node biopsy. H&E staining of cervical lymph node, (A) low-power field and (B) high-power field.

and p63 were totally negative (Fig. 3D-F). Morphologically and immunohistochemically, GCT (embryonal carcinoma) was highly suspected (Figs. 2 and 3). Based on these results, this patient was diagnosed with extragonadal embryonal carcinoma with multiple lymph node and lung metastases. Although isochromosome 12p was not checked and the primary site could not be confirmed, the primary site was considered to be the mediastinum because the size of the mediastinal lymph node metastases was the largest and cervical lymph node metastases were symmetrical in this patient.

About one month after referral to our hospital, this patient developed bilateral recurrent laryngeal nerve paralyses due to enlarged cervical lymph nodes and was hospitalized. Aspiration pneumonia and respiratory failure occurred.

Thus, a tracheotomy was performed, and respiratory support by continuous positive airway pressure was started. On the following day, chemotherapy (BEP: Bleomycin 30 mg on days 1, 8, and 15; etoposide 100 mg/m^2 on days 1-5; and cisplatin 20 mg/m^2 on days 1-5) for extragonadal GCT was started. Administration of granulocyte colony-stimulating factor (G-CSF; filgrastim, 75 μg/day) was begun on day 6 of the first course of BEP therapy. During this course, the patient's neutrophil count decreased (Grade 4) on day 12, and he developed pneumonia requiring management in the intensive care unit. On the same day, the dose of filgrastim was increased to 150 μg/day, and antibiotics including vancomycin and piperacillin/tazobactam were started with mechanical ventilation support. He recovered quickly on day 15, and the subsequent
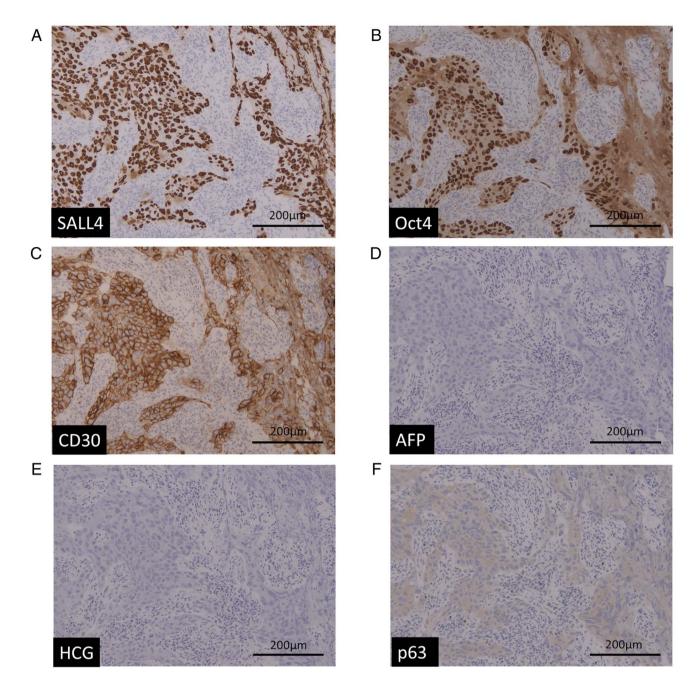
Figure 3. IHC staining results. IHC staining for (A) SALL4, (B) Oct4 and (C) CD30. All are positive. IHC staining for (D) AFP, (E) HCG and (F) p63 are totally negative. IHC, immunohistochemical; CD, cluster of differentiation; SALL4, Sal-like protein 4; Oct4, octamer-binding transcription factor 4.

courses of BEP treatment were continued with prophylactic G-CSF (filgrastim 150 μg/day) support. During the first and second courses of BEP treatment, bleomycin administration was skipped on day 15 due to pneumonia and grade 4 neutropenia. However, four courses of the BEP regimen were completed as scheduled two months later. Contrast CT after three weeks of these interventions showed partial response according to the Response Evaluation Criteria in Solid Tumors (RECIST). PET-CT showed no uptake around the tumor lesions, and this patient was followed closely without further treatment. Due to dysphagia caused by bilateral recurrent laryngeal nerve paralyses, percutaneous endoscopic gastrostomy was performed one month after BEP therapy was ended. Swallowing training was started, and the patient was discharged four months after chemotherapy was started.

One month after discharge, this patient developed facial erythema aggravated by sunlight exposure. The use of allopurinol was stopped due to a suspected drug-induced dermatologic adverse event, but the erythema was not improved. Bilateral periorbital edema and an erythematous eruption over the extensor surfaces of bilateral fingers, or Gottron's sign, appeared subsequently with an elevated CK level (562 U/L). Skin biopsy of the facial erythema showed superficial perivascular dermatitis with mucin deposition, consistent with DM. This patient was referred to another hospital for investigation and treatment. Although the embryonal carcinoma maintained partial response at this time, the distinct skin lesions with the results of the biopsy and the positive anti-TIF-1γ-antibody result confirmed the diagnosis of DM. Laboratory data at that time are shown in Table II. After starting prednisolone (1 mg/kg=70 mg/body daily), the erythema

Table II. Laboratory data when dermatomyositis occurred.

A, Complete blood cell

Variable	Value	Unit
WBC	6,100	/μl
Stab+Seg	51.6	%
Lymphocyte	28.9	%
Monocyte	16.9	%
Eosinophil	2.1	%
Basophil	0.5	
RBC	373	10^4/μl
Hgb	12.2	g/dl
PLT	192,000	/μl

B, Biochemistry

Variable	Value	Unit
TP	6.7	g/dl
Alb	3.6	g/dl
LDH	273	IU/l
T-Bil	0.5	mg/dl
AST	55	U/l
ALT	27	U/l
ALP	229	U/l
γGTP	30	U/l
CK	562	U/l
BUN	22.0	mg/dl
Cr	0.88	mg/dl
eGFR	71.4	ml/min/l
Na	138	mEq/l
K	4.7	mEq/l
Cl	102	mEq/l
Ca	9.7	mg/dl
CRP	0.88	mg/dl

WBC, white blood cell; RBC, red blood cell; Hgb, hemoglobin; PLT, platelet; TP, total protein; Alb, albumin; LDH, lactate dehydrogenase; T-Bil, Total bilirubin; γGTP, gamma glutamyl transpeptidase; CK, creatine kinase; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein.

improved, and his prednisolone is being carefully tapered to prevent the recurrence of DM. The post-chemotherapy surgery was omitted because there were multiple lymph node metastases that had been shrinking without uptake on PET-CT. Over the course of the DM, the extragonadal GCT has maintained a partial response. So far, the relapse-free survival and overall survival of this patient after BEP treatment are both sixteen months without recurrence or death.

Discussion

It is well known that the risk of malignancy in inflammatory myopathy patients is high (6). Although the pathophysiology of malignancy-associated inflammatory myopathy has not yet been determined, many lines of evidence support the relationship of these two different diseases and have shown the incidence, outcome, and prognosis. In inflammatory myopathy, the risk of malignancy differs between DM and PM. The relative ratio of malignancy is approximately 2.4-7.7 times in DM patients and 1.4-2.1 times in PM, respectively. Thus, the relative risk of malignancy is generally higher in DM patients than in PM patients (3-5). The type of malignancy associated with DM and PM is wide-ranging. Ovarian, lung, gastrointestinal, and pancreatic cancers and non-Hodgkin lymphoma are frequently seen in DM patients, and non-Hodgkin lymphoma and lung and bladder cancers are relatively common in PM patients (5). In Japanese patients, gastric, colon, and ovarian cancers are frequently seen in inflammatory myopathy patients (7). However, these population-based studies did not identify GCT patients, and GCT with these myopathies is extremely rare. Only a few cases of GCT including testicular tumors have been reported in association with DM and PM (Table III).

In inflammatory myopathies, several auto-antibodies have been detected. In particular, anti-TIF1γ antibody and anti-NXP2 antibody are known to be associated with malignancy (8). A meta-analysis of six studies involving 312 adult DM patients with malignancy showed that anti-TIF1γ antibody has sensitivity of 78% and specificity of 89% for making a diagnosis of cancer-associated DM (9). The positive anti-TIF1γ antibody result in the present case supports the diagnosis of paraneoplastic inflammatory myopathy though the causal relationship cannot be confirmed only through this test (9). There has been only one case of GCT with autoinflammatory myopathy that was anti-TIF1γ antibody-positive, and more cases are needed to discuss the relationship between this antibody and DM in GCT patients (10).

The prognosis of DM and PM with malignancy has been reported to be worse than with typical DM/PM without malignancy (11). However, rather than other solid tumors in the advanced stage, the prognosis of GCT is relatively better. Thus, the prognosis and complications of this patient group should be more precisely determined.

In our review of previous reports, 17 cases mentioning the relationship between GCT and inflammatory myopathy were identified (Table III). The primary site of 15 cases was testis, and that of two cases was extragonadal (retroperitoneum). Pathological results included seminoma, teratoma, intratubular GCT, mixed GCT, and embryonal carcinoma. Only two cases (12%) had PM, and most cases were associated with DM. As for the timing of onset, five cases (29%) developed myopathy after treatment for the malignancy. Given these results, the present case appears to be the first case of extragonadal GCT with DM that occurred after treatment for the malignancy. The treatment strategy for paraneoplastic inflammatory myopathy varies from corticosteroid administration to treatment of the malignancy, depending on each case. Although the prognosis of inflammatory myopathy with malignancy is generally poor, cases with GCT seem to have a good prognosis, presumably due to the good prognosis of the GCT itself.

To the best of our knowledge, this is the first case of extragonadal GCT with DM that occurred after chemotherapy was completed and during the period of tumor responsiveness. A delayed diagnosis of DM and PM would decrease the quality of life and negatively affect the survival of a patient. The unique clinical course of the present case reminds us that

Table III. Reported cases of germ cell tumor with inflammatory myopathy.

Case	Age	Stage	Pathological diagnosis	Primary site	DM/PM	Treatment for myopathy	Control of myopathy	Best response of cancer	Myopathy before/ after malignancy	(Refs.)
1	30	II	Non-seminomatous GCT	Testis	DM	PSL	Bad	CR	After	(12)
2	30	II	Non-seminomatous GCT	Testis	DM	PSL+AZA+CPA	Good but relapsed	CR but relapsed	Before	(13)
3	28	I	Teratoma, undifferentiated	Testis	DM	PSL	Good	PD	After	(14)
4	30	IIIB	Teratoma, undifferentiated	Testis	DM	PSL	Good	CR	Before	(14)
5	24	II	Mature teratoma, intestinal epithelium and intratubular GCT	Testis	DM	PSL, Chemotherapy	Good	CR	Before	(15)
6	24	II	Intratubular GCT	Testis	DM	PSL	Good	CR	Before	(16)
7	31	III[a]	Embryonal cancer	Testis	DM	Chemotherapy	Good[a]	CR	After	(17)
8	46	IIA	Seminoma	Testis	DM	PSL	Good	CR	Before	(18)
9	29	III	Seminoma or Embryonal carcinoma	Retroperitoneum	DM	PSL+MTX, Chemotherapy	Relatively Good	CR but relapsed	Before	(19)
10	31	IIIB	Embryonal carcinoma	Testis	DM	Chemotherapy	Good	CR	Before	(20)
11	34	I[a]	Testicular cancer[b]	Testis	DM	Immunosuppression[b]	Good	CR	After	(21)
12	50	I	Seminoma	Testis	PM	PSL+MTX	Good	CR	Before	(22)
13	37	I	Seminoma	Testis	DM	Orchiectomy, PSL+AZA	Good	CR	Before	(23)
14	36	IB	Mixed (Seminoma and embryonal carcinoma)	Testis	DM	PSL+MTX	Not good	CR	After	(24)
15	32	II	Embryonal carcinoma with intratubular germ cell neoplasia	Testis	PM	Chemotherapy, PSL, IVIg	Not good	CR	Before	(25)
16	30	I	Seminoma	Testis	DM	mPSL+ AZA	Bad	CR	Before	(26)
17	22	II	Non-seminomatous GCT[b]	Retroperitoneum	DM	PSL, Surgery, Chemotherapy[b]	Good	CR	Before	(11)
18	53	II	Embryonal carcinoma	Extragonad[c]	DM	PSL	Good	PR	After	This case

All cases were male. [a]Not clearly documented. [b]Details unknown. [c]Primary site was not detected. DM, dermatomyositis; PM, polymyositis; GCT, germ cell tumor; PSL, prednisolone; AZA, azathioprine; CPA, cyclophosphamide; CR, complete response; PD, progressive disease; MTX, methotrexate; IVIg, intravenous immunoglobulin; PR, partial response.

we should consider the possibility of malignancy-associated inflammatory myopathies when we see dermal and muscular symptoms, even after treatment for the malignancy. Because of its rarity and the lack of clarity regarding its pathophysiology, further cases are needed to understand this paraneoplastic syndrome in GCT.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YF mainly wrote the manuscript and created the figures and tables; NF cared for the patient, provided professional opinions about writing this report, and revised it; AO, KN, MO, STai and JT cared for the patient and reviewed the manuscript; MT contributed to pathological diagnosis, provided professional opinions about pathological discussion and reviewed the manuscript; STak managed the whole project, and reviewed and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Consent for publication was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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