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CASE REPORT

Dermatomyositis associated with pulmonary large cell neuroendocrine carcinoma: A case report

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ABSTRACT

Background: Dermatomyositis - a rare autoimmune myositis – is a disease affecting primarily the skin and muscles which has been correlated with an elevated risk of solid tumors - commonly affecting the ovaries, breast, colon and nasopharynx. However, there is a rare association between dermatomyositis and pulmonary large cell neuroendocrine carcinoma such that in a thorough literature review of published material, only two cases have been reported internationally and none locally. Large cell neuroendocrine carcinoma - in itself, is also a rare malignancy representing only 1-3% of all primary lung carcinomas.
Case Presentation: This is a case of a 53-year-old Filipino female, hypertensive, diabetic, dyslipidemic, hypothyroid - nonsmoker – who presented with an eight-month history of facial erythema, swelling of bilateral metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, and erythema over extensor surfaces of the MCP and PIP joints. She had markedly elevated creatine kinase MM and positive anti-nuclear antibody for which she was prescribed prednisone, which she did not comply with. She lost weight and experienced severe abdominal pain. Abdominal imaging subsequently revealed multiple confluent abdominal and thoracic lymphadenopathy with histopathology of large cell neuroendocrine carcinoma (LCNEC). Peculiar to this case however is that despite being a lung carcinoma, the scan showed no pulmonary masses or nodules. Immunohistochemical stains of the lymph node were positive for neuroendocrine markers: pancytokeratin, synaptophysin, TTF-1 and negative for any mutation in the epidermal growth factor receptor. Her Ki-67, which is used as a prognostic factor and correlates with mitotic count - was 70% and PD-L1 tumor proportion score – a predictor of therapeutic effect - is 5-10%. She was subsequently diagnosed with dermatomyositis and pulmonary LCNEC. She has presently completed her 8th cycle of cisplatin and etoposide and has gained weight. Presently, her musculocutaneous lesions have resolved. However, a repeat PET scan was done still showing multiple confluent paraaortic, aortocaval, pericaval lymph nodes with no significant interval change from the first PET scan. Next generation sequencing had been requested showing DIS3 to be the gene altercation – however, as of this writing, no available therapeutic modalities are available to target this. Patient was nonetheless given Pembrolizumab for 3 cycles and subsequently expired due to complications of pneumonia.
Conclusion: Among published data, we herein present the third reported case of dermatomyositis associated with pulmonary large cell neuroendocrine carcinoma worldwide and the first reported case in the Philippines thereby contributing to the present medical literature. This case demonstrates two rare diseases associated with each other and exemplifies the need for an awareness of such disease entities. It demonstrates a rare case of LCNEC peculiarly without any pulmonary masses or nodules. It also illustrates the necessity in evaluating patients with dermatomyositis for their respective risk in terms of malignancy and other immunocompromised states. Lastly, it contributes to the knowledge on therapeutic options that may be given to patients presenting with both disease entities.

Introduction

Dermatomyositis is a rare autoimmune inflammatory myositis with a worldwide prevalence of 5 to 22 per 100,000 people - affecting a bimodal age group of 5 to 15 years and 45 to 60 years - with a female predilection. It is a myopathy primarily affecting the skin and muscles that typically presents as symmetric, proximal muscle weakness. Pathognomonic of these patients, are an erythematous rash with papules on the extensor aspects of the digits (Gottron's papules/sign) and/or violaceous rash on the eyelids (Heliotrope rash). Other patients may also present with erythematous rash on the face, knees, elbows, malleoli, neck, anterior chest (V-sign), and back and shoulders (shawl sign) [1] It has been reported that dermatomyositis is associated with a 17.2% increased risk of malignancy most commonly ovarian, breast, colon, nasopharyngeal (in Asians), and non-Hodgkin's lymphoma [2,3] Although still inconclusive and unclear, it is proposed that the association between dermatomyositis and malignancy is secondary to crossover immunity whereby autoimmune response against cancer cross-reacts with regenerating muscle cells. Nonetheless, the association between large cell neuroendocrine carcinoma is rare such that in a systematic review done from 1947 to 2015, only 2 cases of dermatomyositis associated with large cell neuroendocrine tumor was recorded [4].

Large cell neuroendocrine carcinoma is a rare malignancy in itself, affecting approximately 1-3% of all lung cancer cases. Most cases are male and occur at a median age of 66 years old. This malignancy is seen as a mass in the peripheral lung in 80% of cases [5]. According to the current WHO criteria, diagnosis is established when the following criteria are met: (i) neuroendocrine morphology (trabeculae, palisading, organoid nesting and/or rosette formation), (ii) high proliferation rate (>10 mitoses per 10 high-power fields), (iii) extensive geographic necrosis and (iv) expression of at least one neuroendocrine marker (chromogranin-A, synaptophysin, NCAM/CD56) [6].

Herein, we present a case of 53-year-old female who presented with erythema of the face and upper extremities subsequently diagnosed with dermatomyositis and metastatic pulmonary large cell neuroendocrine carcinoma.

Case

This is a case of a 53-year-old Filipino female, known hypertensive, dyslipidemia diabetic, hypothyroid, nonsmoker, with unremarkable family history who initially presented with an 8-month history of constant erythema noted on the face, predominantly seen in the nose, neck and upper trunk

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associated with pruritus. Despite antihistamine intake and other topical interventions, the facial erythema allegedly lessened but remained pruritic. After two months, 6 months prior to consult, she suffered from swelling and pain of bilateral metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints with erythema of the extensor surfaces of the MCP and PIP joints (Figure 1). These were associated with proximal muscle weakness of bilateral knees more prominent in the morning described as difficulty rising from the chair/bed and difficulty in climbing stairs. She further had progression of weakness and pain in the lower back which would intermittently be relieved by taking NSAIDs.

Consult was subsequently sought and diagnostics were done that showed normal CBC with a Hgb 13.3 Hct 40.7, BUN and Creatinine were also noted to be normal however, elevated CPK-MM 1367 IU/l (N: 30-119IU/l), elevated CPK-Total 1448 (N: 30-135IU/l) and elevated ANA 3.5 (N: 1.0-1.2) was reported. Urinalysis was also done with no signs of pus, hematuria, casts or bacteriuria. During this time, she also started losing weight. Prednisone at an unrecalled dose was prescribed for a probable lupus but the patient was non-compliant. At this point, there were no suspicious symptoms of fever, dysphagia, dyspnea, abdominal pain, urinary or gynecologic changes that would point to probable malignancy or infectious disease.

However, one month prior to consult, she suffered from severe postprandial abdominal pain (epigastric to right upper quadrant in location) and upon workup, CT scan revealed multiple thoracic and abdominal lymphadenopathy. Biopsy of a gastrohepatic lymph node was subsequently done showing microscopic findings of "totally effaced architecture and an atypical small round cell infiltrate with a diffuse pattern of growth composed of neoplastic lymphoid cells having ovoid enlarged hyperchromatic to vesicular nuclei, open chromatin, prominent nucleoli and scant to moderate amounts of cytoplasm". Immunohistochemical stains were positive for neuroendocrine markers of pancytokeratin, synaptophysin and TTF-1 and was negative for CD45, CDX2, CEA and CA 19-9 - correlating with large cell neuroendocrine carcinoma. It is known that TTF-1 immunostaining shows a clear mutual exclusivity to identify LCNEC subgroups. Other studies have also demonstrated a specificity of 97 to 100% in establishing a carcinoma of lung primary for this IHC. Her Ki-67, which is used as a prognostic factor and correlates with mitotic count - was 70% and PD-L1 tumor proportion score – a predictor of therapeutic effect - is 5-10%.

A whole body PET CT scan with contrast was subsequently done to evaluate the extent of disease prior to starting chemotherapy and this revealed multiple confluent lymph nodes in the mediastinal, retrocrural, mesenteric, celiac, paracaval, aortocaval, para aortic and left iliac regions with an SUVmax of 18.8 (Figure 2). Despite the finding of LCNEC on immunohistochemical staining, PET CT scan showed no pulmonary masses nor nodules.

In the interim, the patient noted persistence of erythema and swelling over the MCP, PIP and DIP hence, sought consult with another rheumatologist

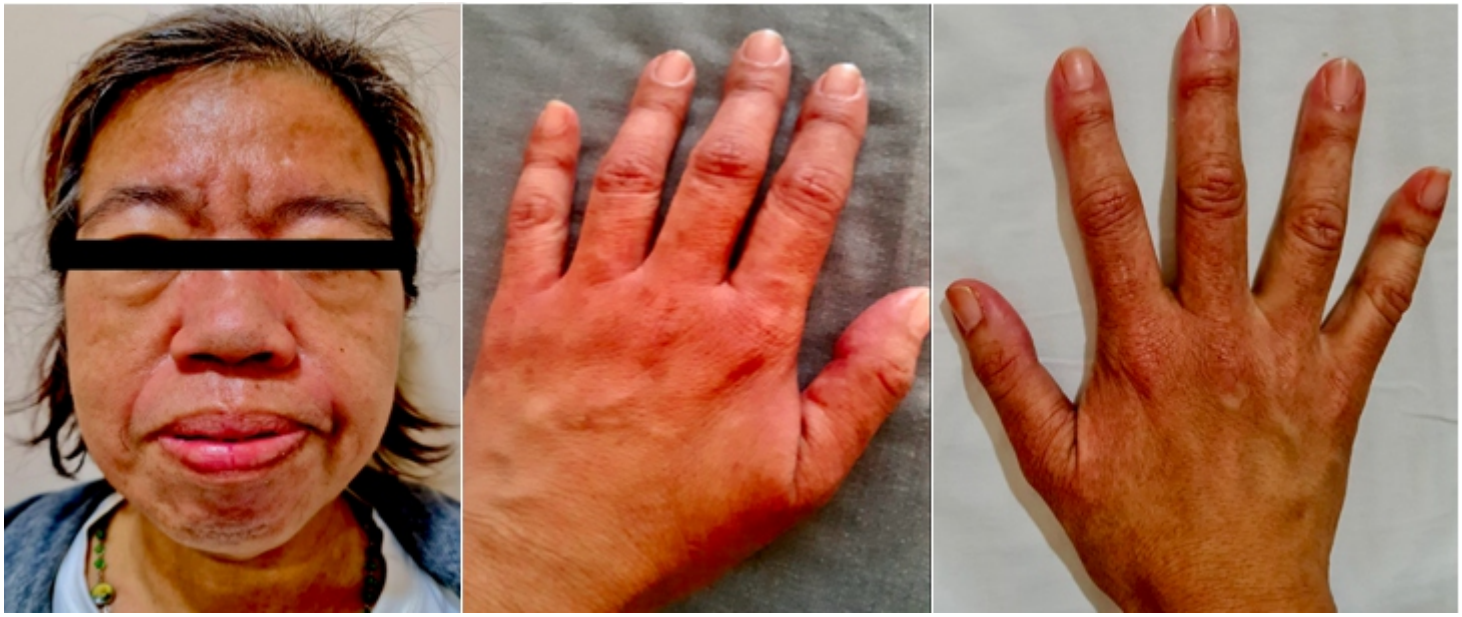

Figure 1. Photo shows erythema over the patient's face (left photo) prior to starting prednisone and chemotherapy. The patient's hand showed prominent erythema and swelling over the MCP, PIP and DIP prior to the treatment (middle photo). After just one cycle of cisplatin plus etoposide and a month of prednisone, we noted almost complete resolution of the swelling and erythema (right photo).

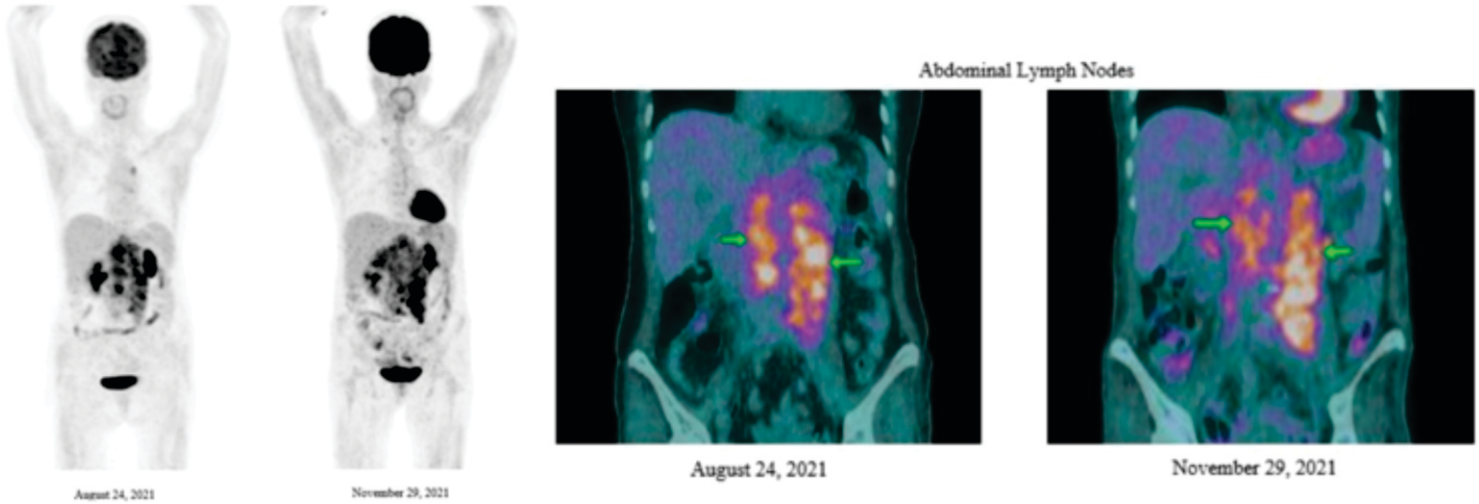

Figure 2. Comparative Whole body PET CT scan prior to initiation of chemotherapy dated August 24, 2021 and after 8 cycles of chemotherapy with Cisplatin + Etoposide dated November 29, 2021 showing multiple confluent paraaortic, aortocaval, pericaval lymph nodes.

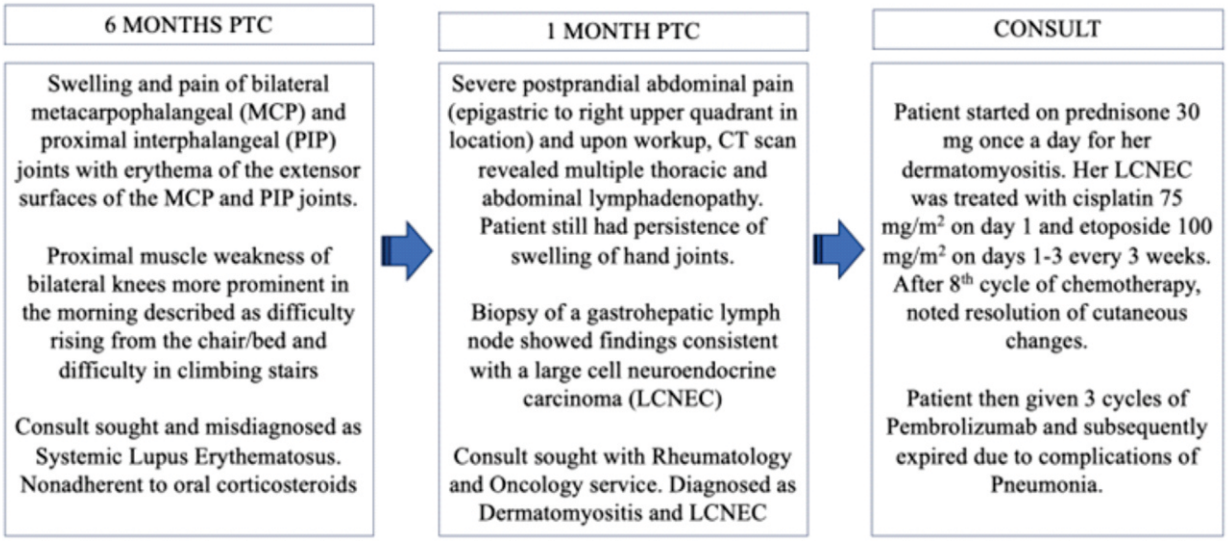

Figure 3. Presents an organized timeline of events from the patient's symptoms to therapeutic management given on consult.

whereby she was reassessed to have probable dermatomyositis. The diagnosis of probable dermatomyositis was made as the patient fulfilled typical cutaneous changes, proximal muscle weakness and elevation of skeletal muscle enzymes. She was not advised to do a skin biopsy and was encouraged to undergo urgent chemotherapy instead. She was started on prednisone 30 mg once a day for her dermatomyositis. Her LCNEC was treated with cisplatin 75 mg/m2 on day 1 and etoposide 100 mg/m2 on days 1-3 every 3 weeks. However, she suffered from CTCAE grade 3 neutropenia after her first cycle and her dose was decreased by 25%. She was also supported with peg-filgrastim and regular filgrastim.

After her 8th cycle of Cisplatin + Etoposide, her musculocutaneous lesions were noted to have resolved. She denies any pain or any difficulty in eating. A repeat PET CT scan was also done after the 8th cycle of chemotherapy showing interval non-demonstration of FDG avid paraaortic and paraesophageal lymph nodes but remains to show multiple confluent paraaortic, aortocaval, pericaval lymph nodes with no significant interval change from the previous.

Next generation sequencing had also been done showing a Tumor Proportion Score (TPS) 0%. Microsatellite status was noted to be stable; however, there was a total of 5 mutational burden noted. The gene that had been implicated in the study was the DIS3. However, for this study, there are no therapies available to target this alteration. Nonetheless, Pembrolizumab was given for a total of 3 cycles. However, after the third cycle, she experienced gradual generalized weakness and developed fever episodes. She subsequently expired due to complications of pneumonia. Figure 3 presents an organized timeline of events from the patient's symptoms to therapeutic management given on consult.

Case Discussion

Five major criteria are used to define dermatomyositis: symmetrical weakness of the limb-girdle muscles, muscle biopsy evidence of necrosis, elevation in serum of skeletal muscle enzymes, EMG abnormalities, and dermatologic features. To definitively diagnose dermatomyositis, three of the four above criteria should be met. However, if only two criteria plus dermatologic signs are met, probable dermatomyositis is diagnosed and if only one criterion plus dermatologic sign is met, then possible dermatomyositis is diagnosed. In our patient, probable dermatomyositis was diagnosed simultaneously with pulmonary large cell neuroendocrine carcinoma. In this case report, the patient fulfilled the diagnosis for probable dermatomyositis and is the first reported case in the Philippines that shows the associated between dermatomyositis and large cell neuroendocrine carcinoma.

Dermatomyositis is associated with various types of malignancy – the prevalence of type of malignancy differs per region. In Asia, particularly in Taiwan, dermatomyositis was associated with cancers of the nasopharynx (66-fold increase), the lung (31 fold increase) and breast wherein two thirds of the comorbid malignancy was detected shortly after diagnosis of dermatomyositis [6]. This is similar to the presentation of our patient wherein her musculocutaneous manifestations presented months prior to her diagnosis of LCNEC. Although still unclear, a model of crossover immunity in the development of cancer associated myositis is being considered as the mechanism behind the association of DM and LCNEC whereby autoimmune response against cancer cross-reacts with regenerating muscle cells.

In this regard, in addition to routine physical and laboratory examination, in patients who present with idiopathic inflammatory myositis (IIM), it has been suggested that a complete blood count, fecal occult blood test, urine assay, whole abdominal ultrasound, upper GI endoscopy and colonic endoscopy can be done to screen for a possible occult malignancy. Our study continues to enjoin in increasing awareness in the importance of individually tailored screening for malignancy in IIM patients according to age, sex, and ethnicity. Other studies have further noted to conduct thorough physical examination and laboratory workup for detecting malignancy for at least 5 years following the diagnosis of IIM especially in dermatomyositis [12].

In terms of treatment approach, according to the American Society of Clinical Oncology Clinical Practice Guidelines for patients with pulmonary large cell neuroendocrine carcinoma, a platinum plus etoposide or the same treatment as other patients with small cell lung carcinoma (SCLC) may be administered since LCNEC share the same clinical behavior with SCLC [7]. For our patient, we gave cisplatin and etoposide and we noted immediate resolution of her erythema and muscle weakness.

In a systematic review of 17 dermatomyositis cases associated with lung neuroendocrine tumor (comprising of 15 cases of SCLC and 2 cases of LCNEC), these patients were given corticosteroids alone, corticosteroids and azathioprine, intravenous immunoglobulin alone, or IVIg and corticosteroids. In both studies, LCNEC was noted to have been related to a solid pulmonary tumor in the lungs or the pleura. However, in the case of our patient, no pulmonary masses or nodules were found - only signs of lymphatic confluence had been noted. Nonetheless, in the systematic review, all treatment approaches showed prompt to gradual response of cutaneous manifestations. It was further noted that in most of these cases, there was symptom resolution of dermatomyositis despite the final prognosis being poor for the underlying malignancy [4].

In the case of our patient, she was noted to have initial good response to platinum + etoposide; however, after her 8th cycle of chemotherapy, post PET CT scan, Pembrolizumab was considered. In a previous systemic review of treatment modalities for LCNEC, Pembrolizumab was used in a study in 2017 achieving partial response in a 64/M with a PDL-1 Tumor Proportion Score of <1% and in 2021 achieving complete response in a 65/M with a PDL-1 Tumor Proportion Score of 40%.11 Further studies are needed in order to determine the outcomes of patients with LCNEC treated with Pembrolizumab.

Table 1. Published cases of dermatomyositis with associated large cell neuroendocrine carcinoma and their response to therapy

Case	Year	Age/ Gender	Diagnosis	Therapy	Response to cutaneous manifestations	Response to muscular manifestations	Survival
Murakami, *et al*[8]	2004	52/M	LCNEC	Prednisolone → Chemotherapy	Marked improvement	Marked improvement	12 mo
Takashima, *et al*[4]	2017	75/M	LCNEC	Prednisolone → Chemotherapy	Gradual improvement	Rapid improvement	18 mo

Conclusion

Among published data, we herein present the third reported case of dermatomyositis associated with pulmonary large cell neuroendocrine carcinoma worldwide and the first reported case in the Philippines thereby contributing to the present medical literature. This case demonstrates two rare diseases associated with each other and exemplifies the need for an awareness of such disease entities. It demonstrates a rare case of LCNEC peculiarly without any pulmonary masses or nodules. It also illustrates the importance of screening patients with dermatomyositis for malignancy and other immunocompromised states. It further adds to the growing literature on therapeutic options that may be given to patients presenting with both disease entities.

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