Dermatomyositis: a debilitating paraneoplastic phenomenon following a diagnosis of localised squamous cell carcinoma of the cervix

Victoria Floyd-Ellis, Alexandra Taylor

SUMMARY
This case report describes the management of a patient, recently diagnosed with Stage IIIC cervical cancer, presenting with significant proximal muscle weakness, dysphagia and cutaneous changes over the hands, knees and outer thighs bilaterally. Following multiple investigations, this clinical presentation was proven to be dermatomyositis as a paraneoplastic phenomenon, a rare diagnosis with cervical cancer. Improvement of the presenting symptoms followed commencement of radical chemoradiation to the primary tumour plus administration of high dose steroids and intravenous immunoglobulins. As demonstrated in this case, and accompanying literature review, dermatomyositis is a rare complication of cervical cancer but should be considered as urgent treatment of the underlying malignancy is imperative. Involving members of the multidisciplinary team, including dieticians and physiotherapists, is of utmost importance to optimise the patient’s recovery from such a debilitating diagnosis.

BACKGROUND
Dermatomyositis (DM) is a microangiopathy affecting skin and muscle; activation and deposition of complement causes lysis of endomysial capillaries and muscle ischaemia, resulting in a cutaneous rash and muscle weakness.1 This presentation as a paraneoplastic phenomenon has become better recognised in recent years, most commonly with ovarian, lung, pancreatic, stomach and colorectal cancers plus non-Hodgkin’s lymphoma. In the majority of paraneoplastic cases, DM precedes the neoplasm.2

A Scandinavian multinational study encom- passing 198 cases of paraneoplastic DM (2001) found only two were associated with squamous cell carcinoma (SCC) of the cervix.2 A further cohort study of 1012 patients with DM, in Taiwan between 1997 and 2007, revealed only three patients with an incidence of cervical cancer.3

We present, here, a rare case of DM diagnosed as a paraneoplastic phenomenon 3 weeks post-diagnosis of human papilloma virus associated SCC of the cervix.

CASE PRESENTATION
A female in her 70s presented with postmenopausal paravaginal bleeding alongside slowly progressing weakness in her shoulders. Following urgent investigation, she was diagnosed with stage IIIC SCC cervix with a 5 cm cervical tumour and 3 cm internal iliac lymph node. She was deemed performance status 1 and planned for radical chemoradiotherapy.

Three weeks following this diagnosis, the patient presented acutely with poor oral intake secondary to dysphagia, plus difficulty living independently as a result of significant proximal muscle myopathy.

On arrival, she appeared dehydrated, her voice was hoarse and speech slowed. Examination revealed a macular rash of purple/red discolouration over the metacarpophalangeal joints, outer thighs and knees bilaterally, muscle wasting of shoulder girdles and marked proximal muscle weakness; MRC (Medical Research Council) power grade 2/5 in shoulder abduction and hip flexion bilaterally. There was no stridor or cough. Cranial nerves I–VIII and XII were grossly normal. Tone, reflexes, light touch, proprioception and pain were normal throughout. The patient was unable to stand from a chair, brush her hair nor climb the stairs without assistance.

Prior to this admission, the patient lived independently in a two-storey home. She required no assistance with activities of daily living, ate a normal varied diet and continued to enjoy hobbies, including riding a bicycle up to 5 km on a weekly basis.

Medical history included osteoporosis and hypothyroidism requiring Aledronic Acid once weekly, Calcichew D3 supplements and Levothyroxine on a daily basis.

INVESTIGATIONS
Haematology and biochemistry
A routine blood panel on admission highlighted multiple raised inflammatory markers, those most notable are listed in table 1.

- Serum vitamin D, Thyroid Stimulating Hormone, free T4, T12 and folate were replete.
- Serum immunology results are shown in table 2.

Imaging
MRI of thighs bilaterally: diffuse heterogeneous, predominantly high T2 signal throughout the pelvic girdle and thigh muscles associated with marked subcutaneous fat stranding and oedema. Appearances were non-specific for inflammatory or oedema.

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Pathology

Biopsy of macular rash from lateral aspect left thigh: basal spongiosis, vacular degeneration and mild perivascular lymphocytic infiltrate. No dysplasia or malignancy seen. Mildly increased dermal mucin present on ABPAS (Alcian Blue Periodic acid Schiff) staining.

Figure 1 shows corresponding histopathology slide.

Speech and language therapy review

On admission, double swallow was noted on liquid and solid consistencies. Throat clearing on both consistencies—straight away with each water sip, throat clearing started after eighth spoon of yoghurt and then periodically during rest of trial increasing towards the end. Clear voice post throat clears.

Hypothesis is that throat clearing is protective, and patient is sensitive to possible penetration±aspiration.

Lung function assessment

A baseline lung function assessment was performed shortly after admission. There were no concerns regarding breathing at this point but given the possibility of deterioration, secondary to DM, it was deemed important to establish the patient’s baseline for comparison.

Result: Mild reduction in vital capacity (VC Max). Spirometry suggests no significant airflow limitation.

OUTCOME AND FOLLOW-UP

There was progressive improvement in symptoms throughout admission; by day 27 all cutaneous lesions, namely Gottron’s papules and Holsters sign, had resolved and the patient was again independent of personal care.

Dysphagia led to an extended period as an inpatient given the need for assistance with oral intake and to minimise aspiration risk. Fifty-five days post admission, she was deemed medically fit and safe for discharge to her own home.

On review 1 month post-discharge, the patient had good movement in her arms and, although still very fatigued, was mobilising well. She returned to her usual diet with no swallowing difficulty and no evidence of cutaneous changes were found on examination. Prednisolone was continuing to be reduced.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Haematology and biochemistry results</th>
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<tbody>
<tr>
<td>Result</td>
<td>Reference range</td>
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<tr>
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<tr>
<td>CK</td>
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<tr>
<td>LDH</td>
<td>140–180</td>
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<tr>
<td>AST</td>
<td>8–33</td>
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<tr>
<td>WCC</td>
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<td>Nts</td>
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<td>Creatinine</td>
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AST, Aspartate Aminotransferase; CK, Creatinine Kinase; CRP, C-Reactive Protein; LDH, Lactate Dehydrogenase; Nts, Neutrophil; WCC, White Cell Count.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Serum immunology results</th>
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<td>Anti SCL-70 antibody</td>
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<tr>
<td>Anti SSA52 Abs (Ro)</td>
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<td>Anti SSA60 Abs (Ro)</td>
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<tr>
<td>Anti SSB Abs (La)</td>
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<tr>
<td>Anti RNP 68 antibody</td>
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<td>Anti RNP A antibody</td>
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<tr>
<td>Anti Sm antibody</td>
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<tr>
<td>Anticentromere B Ab</td>
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<tr>
<td>Anti ds DNA antibody</td>
<td>2.0</td>
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<tr>
<td>Anti-NXP2 Ab</td>
<td>Positive</td>
</tr>
<tr>
<td>Anti-TIF1-γ Ab</td>
<td>Not tested</td>
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</table>

AI, Antibody Index; anti-NXP2, anti-nuclear matrix protein 2; anti-TIF1-γ, anti-transcriptional intermediary factor-1-γ.
On further review 3 months post-discharge, steroids were now discontinued and symptoms continued to improve, so much so the patient was back to undertaking activities as per pre-diagnosis. Imaging with MRI and CT-PET showed a complete oncolgical response to treatment and so regular clinical surveillance continued via 3 monthly assessments.

**DISCUSSION**

DM is a rare, acquired, autoimmune condition. It presents with symmetrical proximal muscle weakness and various dermatological lesions, including but not limited to; Gottron papules, heliotropic rash, facial erythema, Holsters sign and calcinosis cutis. These presentations are thought to be brought about by pathophysiological activation of complement factor 3 (C3) cascading the formation of a membrane attack complex which deposits on vascular walls resulting in inflammation. This causes hypoxic injury, atrophy and necrosis of muscle fibres.

A diagnosis of DM involves correlating clinical presentation with biochemical markers, muscle biopsy and electromyography (EMG). The Bohan-Peter classification of polymyositis and DM is useful in clarifying this. As per this classification, the case presented here would be a \textquoteleft definite\textquoteright DM given the patients cutaneous changes, symmetrical proximal muscle weakness, raised skeletal muscle enzymes and characteristic biopsy. An EMG was not performed as its result would not alter diagnosis nor management plan.

The first reported case of DM as a paraneoplastic phenomenon was recognised by Stertz, who reported inflammatory myopathy in a patient with gastric adenocarcinoma. Paraneoplastic DM is now better recognised, although evidence to quantify just how many DM cases are associated with malignancy is variable; anything between 6% and 60%.

There is strong evidence, however, that paraneoplastic DM as a complication of cervical SCC is rare. A literature search for such cases yielded just four reports, outlined in table 3. Hence, the importance of highlighting the case discussed her include: first, the rarity of paraneoplastic DM in cervical SCC, but also a diagnosis of cancer preceding the development of DM.

A study of 65 patients with paraneoplastic DM in China, 2020, found only 32% of cancers were diagnosed before the occurrence of DM: 14% were within the most recent 1 year, 17% were within 3 years and 23% within 5 years. Another study, published 2001, found only 83 of 198 cases were diagnosed with cancer prior to their diagnosis of DM. This is supported by literature included in table 3, where no patients were aware they had an active cancer when presenting with proximal muscle weakness and cutaneous changes.

Multiple studies highlight the challenge in identifying adult patients with DM at high risk for cancer and how best to investigate such correlation. In March 2022, the British Society for Rheumatology produced a useful guideline highlighting that evidence pertaining to effective cancer screening all idiopathic inflammatory myopathies limited, but suggests CT scanning of the thorax, abdomen and pelvis for at-risk patients is of utility. It defines at-risk patients as those who are; men, older age, of rapid disease onset, experience dysphagia, display cutaneous necrosis or are resistant to immunosuppressive therapy. It also highlights patients with positive anti-transcriptional intermediary factor-1-γ (anti-TIF1-γ) and/or anti-nuclear matrix protein 2 (anti-NXP2) autoantibodies at-risk.

Autoantigen TIF1-γ participates in several biological processes involved in transcriptional regulation, cellular proliferation and apoptosis and in cancer, can act either as a tumour suppressor or promoter, depending on the cellular context and cancer stage. A study by De Vooght et al outlines the hypothesis that mutations or loss-of-heterozygosity in TIF1-γ alleles in malignant tissue drive DM by expression of tumour-specific neo-antigens stimulating autoantibody production to antigens in muscle and skin, hence anti-TIF1-γ autoantibodies should be recognised as a sign of potential underlying tumour autoantigen process.

This is supported by Best et al, whose systematic review and meta-analysis of all relevant published studies confirmed...
Case report

presence of anti-TIF1-γ in adult patients with DM had a 9.37 fold higher risk of cancer than those without.7

In the case discussed here, anti-TIF1-γ antibody presence was not tested given the already known cervical SCC and little diagnostic benefit, however, anti-NXP2 antibodies were tested and found to be positive.

The highest prevalence of anti-NXP2 positive patients with DM with a malignancy reported in a cohort to date is 50%, however, this study conducted in 2012 involved just eight patients.13 Further studies do not draw adequate statistical significance to infer malignancy is more likely in anti-NXP2 positive DM.12 Nevertheless, there is still relevance in this test, given the evidence that anti-NXP2 presence is associated with clinical characteristics that reflect more severe muscle disease activity. Two studies, one in America (2017) and another in China (2021), both conclude adult patients with DM with anti-NXP2 antibodies were more prone to dysphagia, have significantly more severe muscle weakness or higher levels of muscle injury markers and were less likely to present with interstitial lung disease than those without anti-NXP2 antibodies.12 Interestingly, the case discussed here concurs with these findings.

Fortunately, patients with cervical SCC associated DM do appear to experience improvement—if not resolution—of their symptoms, as outlined in this case and those in table 3. The length of time for resolution of muscle weakness varies, possibly in relation to patient age or other factors not compared here, but consistently coincides with treatment of the underlying malignancy. There are multiple discrepancies between the rheumatological treatments administered in the four cases in table 3 and this case, which does not suggest there is no role for these medications but highlights the importance of providing oncological treatments in paraneoplastic DM associated with cervical SCC.

The possibility of drug-related DM in patients with a malignancy is important to consider prior to completing this discussion. There are a number of drugs well-recognised in inducing inflammatory myopathies, HMG CoA reductase (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase) inhibitors, for example, however, those with an underlying malignancy that go on to develop drug-related DM have most commonly been receiving hydroxyurea for chronic myelogenous leukaemia.13 14 This may change with increased use of immune checkpoint inhibitor therapies for malignancies; a review in 2020 highlighted seven published cases of immunotherapy-induced DM, more have been published since.15 16 Clinicians should be aware of the potential of this immunotherapy-related adverse reaction as early recognition and treatment may prevent progression of symptoms, decline of functional status and quality of life.

Patient’s perspective

Having always enjoyed good health and an active life, I was surprised to find that I was beginning to feel tired during the day and that my shoulders kept aching.

Two months later, it came as a shock that I had cancer of the cervix. I was referred to hospital where a treatment plan was formulated. In the intervening weeks, before radiotherapy could be started I found that I couldn’t raise my arms above my head and could barely lift my legs. I was subsequently admitted as an inpatient and underwent many tests by a team of specialists. During those 8 weeks I felt that I was receiving the best of attention and care.

On returning home, I have gradually regained my strength, weight and independence. A recent sensation of numbness in my left foot and lower leg is being monitored.

Learning points

► Paraneoplastic dermatomyositis (DM) associated with cervical squamous cell carcinoma is rare but should be considered in patients who display proximal muscle weakness and cutaneous lesions.
► DM often precedes a cancer diagnosis; the British Society of Rheumatology provides useful guidance on screening for underlying malignancy.
► Ultimately, treating the underlying malignancy is imperative for improvement and resolution of paraneoplastic DM. Additional glucocorticoids, immunosuppressants and intravenous immunoglobulins can also be considered.
► Involving multidisciplinary professionals, including but not limited to; physiotherapists, occupational therapists and dieticians will ensure patients have the best prospect of improving quickly and return to activities of daily living as prior to their DM diagnosis.

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Contributors The following authors were responsible for drafting of the text, sourcing and editing of clinical images, investigation results, drawing original diagrams and algorithms and critical revision for important intellectual content. VFE planned, acquired all included data and supporting information, conducted the literature search and created all content included in this case report document. AT provided ongoing details of the patient’s progress following discharge and kindly reviewed multiple drafts critically for intellectual content and accuracy. VFE and AT gave final approval of the manuscript.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.
REFERENCES
