CASE REPORT

Primary thyroid lymphoma presenting as dermatomyositis: a first case and review of the literature

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Accepted 12 April 2016

SUMMARY

A 55-year-old woman presented with a 3-week history of weakness. On examination, she had a heliotrope rash, V-neck and shawl signs. There was symmetric proximal muscle weakness, and 2/5 strength in upper and lower extremities. Laboratory values showed CK 5836, CRP 14.9, erythrocyte sedimentation rate 49, lactate dehydrogenase 633, negative antinuclear antibodies and anti-Jo1 antibodies. Muscle biopsy and immunohistochemistry findings were consistent with dermatomyositis. Treatment with high-dose steroids, cyclophosphamide and intravenous immunoglobulin (IVIg) was started, without improvement of symptoms. She was found to have cold agglutinins with a cold screen titre of 1:256,256. Work up for malignancy ensued. Positron emission tomography-computed tomography (PET-CT) showed increased uptake in the thyroid. Fine-needle thyroid biopsy with flow cytometry studies revealed atypical lymphocytes consistent with diffuse large B-cell lymphoma. The patient underwent R-CHOP therapy, with remarkable improvement of her symptoms. Dermatomyositis associated with primary thyroid lymphoma has not been previously reported. This case reinforces the importance of cancer screening in dermatomyositis patients.

BACKGROUND

Paraneoplastic syndrome is one of the presentations of dermatomyositis (DM). Approximately 8–15% of adult DM cases have an associated malignancy.^{1 2} The most common DM-associated-cancers are those of the lung, colorectum, cervix and ovary.¹ DM is also associated with a two to fourfold increased risk of non-Hodgkin's lymphoma.¹ Analyses of three Scandinavian cohorts found no significant increase of non-Hodgkin's lymphoma beyond the first 2 years after diagnosis,³ suggesting that the link between DM and non-Hodgkin's lymphoma occurs as a paraneoplastic syndrome. We present a case of a 55-year-old woman with DM who was found to have diffuse large B-cell primary thyroid lymphoma. The patient's symptoms improved after treatment of the underlying malignancy. Our case illustrates classic features of this disorder and the importance of seeking out a possible underlying cancer. This is the first case report of DM presenting as a paraneoplastic syndrome in a patient with primary thyroid lymphoma, in the English Literature.

CASE PRESENTATION

A 55-year-old woman with a history of partial thyroidectomy secondary to thyroid adenoma 20 years prior presented with a 3-week history of progressive generalised symmetric weakness to the point of being unable to walk independently. She required maximum assistance for bed mobility, moderate assistance for transferring and was only able to walk 10 feet with assistance. She also had difficulty swallowing liquid and solid food. She had no other medical history. She had smoked an average of half a pack of cigarettes daily for the past 11 years, and denied use of alcohol and illicit drugs. She denied any history of chemical or radiation exposure. Her brother had been diagnosed with lung cancer in his seventh decade. Review of systems was otherwise negative. The patient had neither fatigue, unexplained weight changes, chest pain, shortness of breath nor palpitation. She also denied having a hoarse voice, constipation, menorrhagia, muscle aches, skin changes or depression.

On examination, she had marked decreased strength in her extremities, with right arm proximal 2/5, distal 3/5, left arm proximal 2/5, distal 3/5, right leg proximal 2/5, 3/5 distal, left leg proximal 2/5 and 3/5 distal. Sensation was intact to light touch, pressure and temperature. She had +2 reflexes in the triceps and biceps bilaterally, and +1 reflexes in the patella and Achilles tendons bilaterally. There was neither palpable lymphadenopathy nor thyromegaly. Diffuse erythematous, non-blanchable patches were noted on her upper chest and back, and under both eyes (figure 1).

INVESTIGATIONS

Laboratory studies revealed haemoglobin 12.7 g/dL (12–16 g/dL), white blood cells 9800/μL (4500–11 000/μL), neutrophils 82% and platelets 255 000/μL (150 000–400 000/μL). Lactate dehydrogenase was 633 U/L (87–225 U/L), antinuclear antibodies were negative, rheumatoid factor was 13 IU/mL (0–13 IU/mL), antithyroperoxidase antibody 21.9 (0–9 IU/mL), thyroid stimulating hormone 4.42 IU/mL (0.27–4.20 μIU/mL), Free T4 1.14 ng/dL (normal range 0.9–1.7 ng/dL), sedimentation rate 49 mm/h (0–20 mm/h), C reactive protein (CRP) 19 mg/dL (0–0.5 mg/dL), creatine kinase (CK) 5836 U/L (26–192 U/L), acetylcholine receptor binding antibody 0.0 nmol/L (0.0–0.4 nmol/L), acetylcholine receptor block antibody 8% (0–26%) and negative anti-Jo1 antibodies. Muscle biopsy revealed perivascular and endomyxial chronic inflammation without lymphocytes surrounding individual myofibres (figure 2).

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To cite: Nan X, Adike A, Rice L, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-215057

Figure 1 (A) Heliotrope rash—well demarcated, non-blanching, violaceous patch around the eyelids. (B) V sign—dusky reddish discoloration of the anterior neck. (C) Diffused erythematous, non-blanchable and poorly circumscribed patches on the back.

Additional immunohistochemistry study of the muscle biopsy revealed C5b-9 focal staining of endomysial capillaries and necrotic fibres (figure 3, compatible with DM).

The patient was initially started on intravenous methylprednisolone 500 mg twice a day for 5 days, immunoglobulin (Privigen 34 g for 5 days) and one dose of cyclophosphamide (304.9 mg/m²) for treatment of DM. Despite treatment, she had only minimal improvement of weakness and the dysphagia worsened. She required maximum assistance for bed mobility, moderate assistance for transferring and was only able to walk 10 feet with assistance. At this point, she was transferred to our institution, where cyclosporine (100 mg twice a day for 12 days) and one dose of rituximab (365.9 mg/m²) were added to treatment. On arrival to our hospital, her haemoglobin was 10.7 g/dL (normal range 12–16 g/dL). Her reticulocyte percentage was 3.7% (normal range 0.5–2.1%). Blood smear showed red blood cell agglutination at room temperature, suggesting cold agglutinin haemolytic anaemia. Cold agglutinin titre was 1:256,256. This finding raised concern for an underlying haematological malignancy. CT of the abdomen and pelvis, and colonoscopy, were normal. A positron emission tomogram revealed diffuse uptake of a right-sided thyroid mass without evidence of activity elsewhere (figure 4). Ultrasound of the thyroid was

consistent with a 3.6×2.4×2.1 cm heterogeneous solid mass in the right lobe (figure 5). Fine needle biopsy of the right thyroid nodule revealed diffuse large B-cell lymphoma (figure 6). Flow cytometry found positive staining for CD20, CD19, CD5, lambda, CD22, CD38 (dim) and CD52. The final diagnosis in our patient was stage 1AE diffuse large B-cell lymphoma with paraneoplastic DM.

OUTCOME AND FOLLOW-UP

The patient underwent chemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) with an additional dose of rituximab on day 8 for the cold agglutination disease. Her symptoms significantly improved after one cycle of R-CHOP chemotherapy. She was able to demonstrate bed mobility and transfer independently, and could walk 120 feet without assistance. After six courses of chemotherapy, she was in complete remission from the lymphoma (PET negative), the cold agglutinin disease and the DM.

DISCUSSION

DM is an inflammatory myopathy, often characterised by symmetric proximal muscle weakness and cutaneous manifestations.

Figure 2 Muscle biopsy (H&E staining, ×200 magnification). (A) Random spectrum of atrophic fibres throughout fascicle with necrotic fibres, regenerating fibres and endomysial fibrosis. (B) Perimysial perivascular chronic inflammation with lymphocytes extending into the adjacent endomysium.

Figure 3 Muscle biopsy immunohistochemistry (A) human leukocyte antigen (HLA) staining slide (x200 magnification): No staining of myofibres. (B) C5b-9 capillary staining slide (x200 magnification): myofibrillar and endomysial capillary staining.

About 8.5–15% of cases of DM in patients over the age of 40 years have an underlying malignancy.² In a meta-analysis, Yang *et al*⁴ found that the risk of malignancy in patients with DM is about 4.5-fold higher than in the general population. This risk is often highest in the first or second year of diagnosis.⁴ Oftentimes, when the underlying malignancy is treated, as in our patient, the symptoms of DM also improve.

Patients with paraneoplastic DM, as in our patient, often present with progressive symmetric muscle weakness, heliotrope rash, Gottron's papules, elevated CK levels and negative anti-Jo1 antibodies. The pathophysiology of inflammatory

myositis and malignancy is not well understood, although there is clearly an immunological process linking malignancy and inflammatory myopathy syndromes. One possible mechanism for paraneoplastic syndrome in patients with DM is that antibodies produced by the body against tumour cells may also destroy normal cells. Inflammatory muscle cells express high levels of myositis-specific antigens, which may also be expressed by several cancer cells.⁵ Paraneoplastic syndrome may also result from physiologically active substances that are released by tumour cells. Another potential mechanism could be that changes in the extracellular matrix of the tumour cause release

Figure 4 PET scan shows diffuse uptake of a right-sided thyroid mass.

Figure 5 Ultrasound of thyroid shows a 3.6×2.4×2.1 cm heterogeneous solid mass in the right lobe. (A) Transverse view. (B) Sagittal view.

of fractions of glycosaminoglycan into circulation, resulting in changes in the extracellular matrix of normal tissue.

Our patient also presented with cold agglutinin haemolytic anaemia. Cold agglutinin haemolytic anaemia is an autoimmune process in which IgM antibodies usually directed against the 'I' antigen cause agglutination of red cells, microvascular occlusion in cooler areas of the body and complement-mediated haemolysis. While in younger patients this is most commonly caused by an infection such as *Mycoplasma* or an autoimmune disease such as systemic lupus erythematosus, the differential diagnosis is quite different in older patients, where underlying lymphoproliferative disorder is very frequent and must be considered; other cases are chronic and idiopathic.

Although there have been several case reports of DM associated with papillary thyroid carcinomas,^{6 7} DM associated with primary thyroid lymphoma has not previously been reported. Primary thyroid lymphomas (PTL) are very rare. PTL is defined as a lymphomatous process involving the thyroid gland, with neither continuous spread nor metastasis to other organs at the time of diagnosis.⁸ These lymphomas make up about 5% of thyroid cancer, and about 1% of non-Hodgkin's lymphoma.⁸ They typically occur in females, with a median age of 60 years.⁹ One reason for the gender predilection could be the association between Hashimoto's thyroiditis and thyroid lymphomas. Hashimoto's thyroiditis increases the risk of thyroid lymphoma by up to 50 times.¹⁰ It takes about 20–30 years to develop after onset of autoimmune thyroiditis.⁸ It is possible that our patient also had a history of autoimmune thyroiditis, given the elevated antithyroid peroxidase antibody. Interestingly, several case reports have described an association between DM and autoimmune thyroiditis.^{11 12} Wang *et al*¹² identified 3 of 11 patients in their

review of DM and autoimmune thyroiditis who had thyroidectomy for nodular goitres before a diagnosis of DM was made. One patient in this retrospective review had non-Hodgkin's lymphoma but it is unclear what nodal sites or organs were involved.

The most common presentation of thyroid lymphomas is rapid swelling in the neck, associated with compressive symptoms of dysphagia, hoarseness or dyspnoea. Our case is unique given that severe proximal weakness was our patient's primary symptom, and she was eventually found to have DM and cold agglutinin disease—the combination of which suggested an underlying malignancy as the primary aetiology of the disease process in this middle-aged woman.

Diagnosis of thyroid lymphomas can be made using fine-needle aspiration with cytology, flow cytometry and immunophenotyping. Up to 70% of thyroid lymphomas are diffuse large B-cell lymphomas (DLBCL) with up to 30% being mucosa-associated lymphoid tissue lymphomas.⁹ The recommended treatment of thyroid lymphomas depends on the histological subtype and stage of disease. Poor prognostic factors include age greater than 60 years, elevated LDH and B2-microglobulin, more than one extranodal site and tumour size greater than 5 cm.⁸ Treatment of DLBCL primary thyroid lymphoma is similar to other nodal lymphomas, and based on R-CHOP therapy. About 90% of patients are failure-free after about three to six courses of this regimen. In more aggressive lymphomas with adverse prognostic factors, a combination of R-CHOP and radiation is recommended.¹³ Radiation was used as an adjuvant in the past, but surgery is generally not indicated.¹⁴ Our patient was treated with six cycles of R-CHOP, and her lymphoma and DM both responded dramatically.

Figure 6 Thyroid biopsy (left: Diff-Quik staining and ×10 magnification; right: papanicolaou staining and ×20 magnification) showing a very cellular background composed of dispersed lymphoid cells. There are also groups of reactive-appearing follicular cells, which are densely infiltrated by lymphocytes.

Learning points

- Our case emphasises the importance of recognizing the connection between adult-onset DM and malignancy.
- Because paraneoplastic DM often improves with the treatment of the underlying malignancy, all patients presenting with adult-onset DM should have an age-appropriate cancer screening and surveillance as well as an individualised screen based on their personal and family history.

Acknowledgements The authors are thankful to Dr Susan Haley and Dr Jamie Jacobsohn, for the contribution of pathology figure preparation and description. The author also thank to Anusha Sunkara, Dr Mirza Baig and Jovan Popovich, for the contribution of draft revision.

Contributors All the authors listed contributed sufficiently to the project to be included as authors, and all those who are qualified to be authors are listed in the author byline. XN, AA and VB were involved in the conception or design. XN, AA, VB and LR were involved in the literature research. XN, AA; LR and VB were involved in the drafting and revising. VB was involved in the supervision.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Sigurgeirsson B, Lindelof B, Edhag O, *et al.* Risk of cancer in patients with dermatomyositis or polymyositis. A population-based study. *N Engl J Med* 1992;326:363–7.
- 2 Callen JP, Hyla JF, Bole GG Jr. The relationship of dermatomyositis and polymyositis to internal malignancy. *Arch Dermatol* 1980;116:295–8.
- 3 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.
- 4 Yang Z, Lin F, Qin B, *et al.* Polymyositis/dermatomyositis and malignancy risk: a meta analysis study. *J Rheumatol* 2015;42:282–91.
- 5 Casciola-Rosen L, Nagaraju K, Plotz P, *et al.* Enhanced autoantigen expression in regenerating muscle cells in idiopathic inflammatory myopathy. *J Exp Med* 2005;201:591–601.
- 6 Shah M, Shah NB, Moder KG, *et al.* Three cases of dermatomyositis associated with papillary thyroid cancer. *Endocr Pract* 2013;19:e154–7.
- 7 Nagashima T, Onishi S, Kamata Y, *et al.* Dermatomyositis associated with thyroid cancer: a paraneoplastic syndrome? *Rheumatol Int* 2009;29:1261–2.
- 8 Gupta N, Nijhawan R, Srinivasan R, *et al.* Fine needle aspiration cytology of primary thyroid lymphoma: a report of ten cases. *Cytojournal* 2005;2:21.
- 9 Verma D, Puri V, Agarwal S, *et al.* Primary thyroid lymphoma: a rare disease. *J Cytol* 2014;2014;31:218–20.
- 10 Holm LE, Blomgren H, Löwhagen T. Cancer risks in patients with chronic lymphocytic thyroiditis. *N Engl J Med* 1985;312:601–4.
- 11 Go T, Mitsuyoshi I. Juvenile dermatomyositis associated with subclinical hypothyroidism due to auto-immune thyroiditis. *Eur J Pediatr* 2002;161:358–9.
- 12 Wang H, Tao L, Li H, *et al.* Dermatomyositis related to autoimmune thyroiditis. *J Eur Acad Dermatol Venereol* 2011;25:1085–93.
- 13 Mack LA, Pasieka JL. An evidence-based approach to the treatment of thyroid lymphoma. *World J Surg* 2007;31:978–86.
- 14 Matsuzuka F, Miyauchi A, Katayama S, *et al.* Clinical aspects of primary thyroid lymphoma: diagnosis and treatment based on our experience of 119 cases. *Thyroid* 1993;3:93–9.

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