Myositis and malignancy: is there a true association?

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There may be an association between polymyositis/dermatomyositis and malignant disease. Cancer occurs in patients with polymyositis/dermatomyositis with a frequency estimated between 2.5% and 29% (relative risk 1.0 to 6.5). We present two such cases, associated with colorectal carcinoma and non-Hodgkin's lymphoma respectively, together with an overview of existing controlled studies in the area.

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The purported association between myositis and malignant disease is largely anecdotal. There is a bias toward reporting cases which support the link and a lack of controlled study into the area, so the nature of the relationship remains uncertain. We present two cases referred to our department recently, with an overview of published controlled studies investigating the association.

DISCUSSION

Dermatomyositis and polymyositis are inflammatory myopathies of unknown aetiology characterized by symmetrical proximal myopathy with or without characteristic skin lesions. They have a progressive, sometimes fluctuant course over weeks or months, with occasional involvement of the oesophagus, small intestine and respiratory musculature. They may respond to

CASE REPORT 1

A previously healthy 52-year-old female presented to a Belgian dermatology department with a 6-month history of an itchy eruption affecting the hands and scalp. A generalized maculopapular rash was noted, with bluish plaques over the hands, elbows and scalp, Gottron's papules and generalized lymphadenopathy. Initial investigations revealed a positive antinuclear factor and normal creatinine kinase (CK), and electromyography demonstrated proximal myopathy. Capillaroscopy was compatible with dermatomyositis. Histology of a skin biopsy was inconclusive. The patient commenced steroids with a provisional diagnosis of dermatomyositis, and the rash remitted. Investigations for underlying neoplastic disease were undertaken: chest X-ray, mammogram, abdominal computed tomography (CT) scan, protein electrophoresis, carcinoembryonic antigen, cancer antigen 125, and gynaecology consultation were normal.

Six months later, the patient presented to this hospital with altered bowel habit and rectal bleeding. Rectal examination and CT abdomen confirmed a rectal adenocarcinoma. She underwent anterior resection, and pathology confirmed a moderately differentiated Dukes A tumour. At that time the rash remained in remission, but 3 months later it recurred (*Figures 1a* and *b*), together with thigh weakness and elevated CK (>3000 u/litre). Muscle biopsy was unremarkable, but skin biopsy confirmed active dermatomyositis (*Figure 2*). The patient recommenced prednisolone 20 mg daily. A month later azathioprine 50 mg daily was added. The patient improved on the above regimen, the steroid being reduced to 10 mg daily. Her further course was complicated by subacute intestinal obstruction resulting from adhesions, settling with conservative management, and a painful hip restricting mobility and requiring opiates. Initial investigations revealed an elevated erythrocyte sedimentation rate (ESR) and white cell count (neutrophilia). X-ray, ultrasound and CT of the affected area were normal; joint aspiration was performed, but the small amount of capsular fluid obtained was sterile on prolonged culture. Pain and loss of function progressed, and repeat X-ray 1 month later showed capsular destruction. Open biopsy confirmed *Staphylococcus aureus* septic arthritis, and the patient commenced 6 weeks of flucloxacillin and fusidic acid. Four months later, she continues to experience proximal weakness, but ESR and CK are normal.

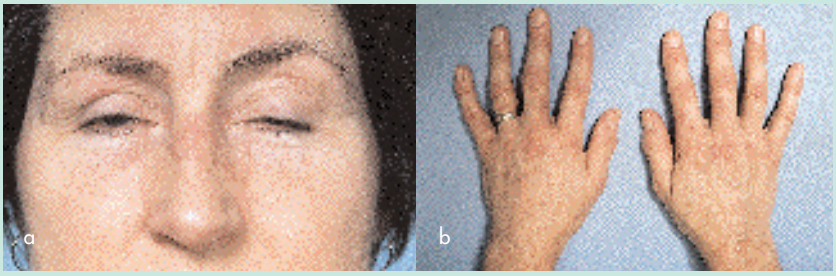

Figure 1. Typical cutaneous features of dermatomyositis. a. Periorbital heliotrope rash. b. Scaling maculopapular rash over dorsum of hands.

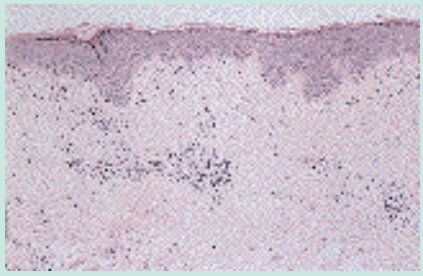

Figure 2. Skin biopsy in dermatomyositis, showing inflammatory infiltrate in the dermal layer.

steroid therapy. Up to 29% of cases, mainly over 45 years of age, have been associated with malignancies in a number of reports. The increased frequency of associated cancer, the temporal relationship between the onset of myositis and cancer, subgroups at increased risk, and tumour types associated are unclear. Epidemiological study has been hampered by small case numbers, lack of controls, referral bias and diagnostic inconsistency, thus hampering a screening strategy (Bernard and Bonnetblanc, 1993; Zantos et al, 1994).

TABLE 1.
Case control studies on myositis and malignancy

		Frequency of cancer (% of patients)		
Reference	**Study type**	**DM**	**PM**	**Control**
Manchul et al (1985)	Case-control	9/31 (29)	7/40 (18)	5/142 (4)
	Cohort	2/31 (7)	1/40 (3)	9/142 (6)
Lakhanpal et al (1986)	Case-control	11/50 (22)	18/65 (28)	20/115 (17)
Lyon et al (1989)	Case-control	1/40 (3)	4/64 (6)	3/104 (3)

DM = dermatomyositis; PM = polymyositis

TABLE 2.
Cohort studies on myositis and malignancy

	Frequency of cancer (% of patients)		Relative risk			
Reference	**DM**	**PM**	**DM**		**PM**	
Sigurgeirsson et al (1992)	61/392 (16)	42/396 (11)	Female 3.4	Male 2.4	Female 1.7	Male 1.8
Chow et al (1995)	31/203 (15)	26/336 (8)	3.8		1.7	
Airio et al (1995)	19/71 (27)	12/175 (7)	6.5		1.0	

DM = dermatomyositis; PM = polymyositis

Tables 1 and *2* summarize six controlled studies investigating the relationship between myositis and malignancy published in the last 12 years. Each of the studies utilize the 1975 diagnostic criteria of Bohan and Peter (*Table 3*).

Three case-control studies (*Table 1*) used subjects identified in single tertiary referral centres or by postal survey, resulting in a highly selected study group (Manchul et al, 1985; Lakhanpal et al, 1986; Lyon et al, 1989).

Manchul et al (1985) identified all cases referred to a Canadian rheumatology department over a 15-year period and compared the prevalence of malignancy at presentation with matched controls. They also performed a cohort analysis of the cancer incidence following diagnosis of myositis compared with age and sex specific cancer rates for the total Canadian population. The case-control arm identified 15 antecedent or concurrent cancers compared with 5 in the control group, but the cohort arm demonstrated no increase in the number of subsequent cancers observed.

TABLE 3.
Diagnosis of myositis

Polymyositis/ dermatomyositis	Symmetrical muscular weakness — limb girdle and anterior neck flexors
	Histology of muscle biopsy
	Elevated skeletal muscle enzymes
	Electromyography pattern
Dermatomyositis only	Heliotrope periorbital rash, Gottron's papules, scaly dermatitis extensor surfaces

From Bohan and Peter (1975)

CASE REPORT 2

A 65-year-old female with a history of angina presented with proximal muscle weakness, fatigue, and difficulty climbing stairs evolving over the previous 2 years. She described no rash, myalgia or systemic symptoms. Initial investigation revealed a normal full blood count, urea and electrolytes, erythrocyte sedimentation rate, and autoantibodies, but the creatinine kinase (CK) was elevated at 2000 u/litre. She was biochemically hypothyroid and was commenced on thyroxine for possible myxoedematous myopathy. At review 3 months later her symptoms had progressed such that she was having difficulty rising from a chair, and now described muscle pain and weight loss. Proximal muscle weakness and sluggish reflexes were present, and additionally craggy cervical lymphadenopathy and hepatomegaly. Further investigation showed normal nerve conduction studies, and an electromyogram was myopathic. Lymph node biopsy showed a high grade T-cell non-Hodgkin's lymphoma, and muscle biopsy confirmed polymyositis (*Figure 3*). She commenced chemotherapy, with prednisolone as part of the regimen.

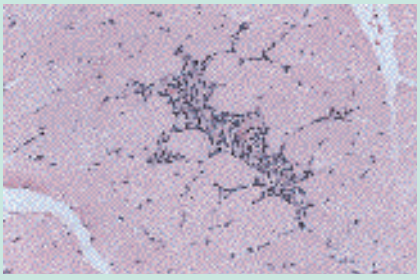

Figure 3. Muscle biopsy in polymyositis. Low power view showing inflammatory infiltrate surrounding muscle fibres.

While undergoing chemotherapy, she was admitted with progressive proximal weakness, with inability to rise from sitting, poor control of the neck musculature and difficulty raising her arms. The CK had risen to 12000 u/litre. Prednisolone 60 mg daily was commenced. Some clinical improvement ensued, CK falling to 500 u/litre. Following intensive physiotherapy she was able to return home.

Two months later, following completion of chemotherapy, the patient was readmitted with progressive weakness. The lymphoma appeared in remission and CK was moderately elevated at 1500 u/litre. The illness was complicated by painful oesophageal dysmotility necessitating a percutaneous enterogastrostomy tube, steroid-related osteoporotic vertebral crush fractures, deep venous thrombosis, and by perineal shingles with post-herpetic neuralgia. The patient subsequently died of pneumonia. Post-mortem showed active myositis with oesophageal involvement and myocarditis but no evidence of recurrent lymphoma.

Lakhanpal et al (1986) identified 115 patients with myositis referred to the Mayo Clinic between 1965 and 1974. Age, sex, and geographically matched controls were identified from the same clinic and the rates of prior, concurrent and subsequent cancer over 10–20 years follow-up were ascertained. Overall, 29 patients with myositis developed cancer compared with 20 controls. This difference was not statistically significant, being attributed to referral and detection bias.

The postal survey by Lyon et al (1989) compared antecedent and subsequent cancer incidence in polymyositis/dermatomyositis patients compared with sibling controls. They found no significant association (5 cancers in the myositis group, 3 in the control).

Three more recent studies (*Table 2*) comprise larger population-based cohort studies from Scandinavia (Sigurgeirsson et al, 1992; Airio et al, 1995; Chow et al, 1995). All patients with clinically suspected myositis were hospitalized for investigation and the subsequent cancer incidence compared with that of age and sex specific rates for the general population by record linkage to the national cancer registry. Follow-up was for an average of 10, 5 and 9 years respectively. Despite different diagnostic methodology, each of these studies demonstrated an increased relative risk (RR) of cancer in relation to dermatomyositis (RR 2.4–6.5), with the risk greatest in the first year following diagnosis (RR 5.9–26) (Airio et al, 1995; Chow et al, 1995). The risk of cancer developing in polymyositis was less pronounced (RR 1.0–1.8), and may have resulted from increased cancer surveillance.

These studies showed similar cancer incidence in both sexes, and cancer was very rare in cases aged less than 45 years.

It has been postulated that a normal serum creatinine kinase is associated with increased risk of malignancy, that presence of other connective tissue disease implies lower risk, and that autoantibodies such as anti-Jo are absent in myositis associated with cancer (Callen, 1994). These hypotheses are based on very small case series or isolated reports.

The three Scandinavian series suggest that, with the exception of ovarian carcinoma, the types of neoplasm occurring in association with dermatomyositis are comparable to an age-matched general population (*Table 4*).

CONCLUSIONS

Current literature suggests that diagnosis of dermatomyositis can point to underlying malignancy, especially in the first year following diagnosis. The association with polymyositis is less clear-cut and may be a result of detection bias. Tumours found reflect those of an age-matched population, with a possible preponderance of ovarian cancer. Screening for malignancy should therefore be concentrated on patients aged over 45 years old with dermatomyositis. This should include a thorough history and clinical examination including rectal, breast, pelvic and testicular examination. In addition to a full blood count, biochemical screen, protein electrophoresis, urinalysis, faecal occult bloods, chest radiograph, and mammogram, tumour markers (CA 125, carcinoembryonic antigen, prostate-specific antigen) and pelvic ultrasound should be considered. **HM**

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Sigurgeirsson B, Lindelof B, Edhag O, Allander E (1992) Risks of cancer in patients with dermatomyositis or polymyositis: a population-based study. *N Engl J Med* **326:** 363–7

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TABLE 4.
Commonest sites of cancer in dermatomyositis

		No of patients (relative risk)			
Reference		**Gut**	**Lung**	**Breast**	**Ovary**
Sigurgeirsson et al (1992)	Male	6 (3.8)	6 (6.5)	–	–
	Female	6 (4.0)	1 (2.6)	9 (3.2)	9 (8.2)
Chow et al (1995)		6 (3.2)	8 (8.4)	3 (2.7)	4 (15.5)
Airio et al (1995)		7 (4.0)	3 (10.0)	1 (1.8)	4 (32.0)

KEY POINTS

- Dermatomyositis is associated with neoplasm.
- Polymyositis may be associated with neoplasm.
- Cancer incidence is greatest in the year following diagnosis.
- Tumour types reflect those of the general population.
- There is a possible increased risk of ovarian carcinoma.
- Cancer screening should be undertaken at the time of diagnosis.