Paraneoplastic Muscle Disease

Alan N. Baer, MD

KEYWORDS

• Malignancy • Myopathy • Dermatomyositis • Polymyositis
• Paraneoplastic • Eaton-Lambert syndrome • Myasthenia gravis
• Stiff person syndrome

Skeletal muscle disease may arise in the setting of malignancy. The potential mechanisms are varied and may include direct invasion of the muscle by an adjacent tumor, the rare occurrence of a skeletal muscle metastasis, muscle injury from chemotherapy or infection, dysfunction from metabolic derangements, and wasting as a result of tumor-related cachexia. The term paraneoplastic is applied when none of these mechanisms are applicable.[1] In paraneoplastic muscle disease, the malignancy may remotely affect neuromuscular transmission or incite muscle inflammation or necrosis. In several of these diseases, an autoimmune basis for the muscle disease has been established and has become a defining feature.[2,3] These paraneoplastic muscle diseases may be the first manifestation of a malignancy, and their diagnosis thus demands a vigilant search for an underlying tumor. This article is focused on inflammatory and necrotizing myopathies and disorders of neuromuscular transmission that may arise in the setting of malignancy and are considered paraneoplastic phenomena.

DERMATOMYOSITIS AND POLYMYOSITIS

Dermatomyositis (DM) has been linked with underlying malignancy since the publication of 2 case reports of this association in 1916.[4,5] A significantly increased risk of a malignancy among patients with DM has now been established from epidemiologic studies, with the risk of malignancy being highest at the time of or within 1 year of diagnosis.[6] The risk of an underlying malignancy is much lower for polymyositis (PM) but remains statistically significant.

Portions of this article have been adapted from Baer AN, Wortmann RL. The risk of malignancy in patients with dermatomyositis and polymyositis. In: Kagen LJ, editor. The inflammatory myopathies. New York: Humana Press; 2009; with permission.

Division of Rheumatology, Johns Hopkins University School of Medicine, Good Samaritan Hospital, 5200 Eastern Avenue, Mason F. Lord Building Center Tower, Suite 4100, Room 413, Baltimore MD 21224, USA
E-mail address: alanbaer@jhmi.edu

Rheum Dis Clin N Am 37 (2011) 185–200
doi:10.1016/j.rdc.2011.01.011 **rheumatic.theclinics.com**
0889-857X/11/$ – see front matter

Epidemiology

The criteria by Bohan and Peter[7] for the diagnosis of PM and DM have been the standard since their publication in 1975, although new criteria are clearly needed.[8] The author identified a total of 35 retrospective case series of inflammatory myopathy in the period between 1975 and 2009 that used these diagnostic criteria and reported the occurrence of malignancy in these patients (**Table 1**). These series from diverse geographic areas include 2326 patients with DM, of whom 557 (24%) had an associated malignancy, and 941 patients with PM, of whom 97 (10%) had an associated malignancy. Carcinomas of the nasopharynx (23%), lung (15%), breast (15%), ovary (8%), colon (5%), stomach (3%), and liver (3%) were the most common malignancies associated with DM.[9,11–16,24,26,30–37,39–41,43–47] There was no predominant tumor type among the limited number of cases associated with PM.

These case series demonstrated that the association with malignancy was much stronger for DM than for PM. These series also highlighted the influence of ethnicity on the types of associated malignancy, the temporal association between the myositis and the malignancy, and the type of evaluation used to recognize the malignancy. These cases were also subject to several forms of bias and thus do not establish a casual link between malignancy and either DM or PM.[48] Almost all cases had a referral bias, using patients seen in tertiary hospitals or specialty clinics. In addition, these cases were subject to Berkson bias; a patient with an occult malignancy who had an associated myopathy was more likely to be hospitalized than a similar patient without myopathy. The bias of increased suspicion and scrutiny for malignancy in patients with PM/DM also existed.

The association of malignancy with DM and PM has been scrutinized in 5 population-based retrospective cohort studies (**Table 2**).[6] In each study, the risk of malignancy in a population-based cohort of patients with PM and DM was compared with that in a normal population. This study design reduced the biases related to referral and diagnostic suspicion of malignancy. In 4 of the studies, all patients with PM and DM hospitalized during a defined period were identified from national hospital discharge databases.[50–53] These studies analyzed cohorts from Sweden, Denmark, Finland, and Scotland, which were ethnically homogeneous. The fifth study identified all cases of biopsy-proven idiopathic inflammatory myopathies in the state of Victoria, Australia during a defined period, using the records of the state reference neuropathology laboratory in which all muscle biopsies results are reviewed.[49] The occurrence of malignancy (excluding nonmelanoma skin cancers) in these patients was determined from national cancer registries and also, in 1 study, from death records for the same period. Malignancies that were identified at the same time or after the diagnosis of myositis were included in the calculation of risk. In some studies, malignancies that were identified during the first 3 to 12 months after the myositis diagnosis were excluded in separate analyses to eliminate diagnostic suspicion bias.[49,51,53]

Each of these 5 studies identified an increased risk of malignancy in patients with DM compared with the general population (see **Table 2**). The overall standardized incidence ratios ranged from 3.8 to 7.7. In addition, 2 of the studies identified an increased but lesser risk in patients with PM, with overall standardized incidence ratios of 1.7 to 2.0.[49,51,52] The cancer risk was increased approximately sixfold during the first year after myositis diagnosis but was lower during the second year, with no significant excess in subsequent years of follow-up.[52] The increased risk of malignancy in DM remained evident when malignancies identified during the first 3 months or the first year after the diagnosis of myositis were excluded.[49,51] Inclusion body myositis was also associated with an increased risk of malignancy in the one study that used muscle biopsy reports for case finding.[49]