Malignancy and Idiopathic Inflammatory Myopathies

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Abstract

Association between idiopathic inflammatory myopathies (IIMs) and malignancy is well known and has been extensively reported in the literature. However, in the recent years, several new studies were published allowing us to better understand the clinical characteristics and pathophysiology of cancer-associated IIMs. We conducted a literature review of cancer-associated IIMs focusing on new data that was published in the recent years.

Keywords: Dermatomyositis, Idiopathic inflammatory myopathies, Malignancy, Polymyositis

Introduction

Idiopathic inflammatory myopathies (IIMs) are chronic systemic autoimmune disorders characterized by progressive proximal muscle weakness. The common subtypes include dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM). The widely accepted diagnostic criteria for DM and PM, which combine clinical, laboratory, and pathological features, were proposed by Peter and Bohan in 1975\textsuperscript{1,2} and remain the gold standard for clinical study.

The association between IIMs and malignancy is well known and has been extensively reported in the literature. This article reviews the literature on this association, focusing on the epidemiological evidence, pathogenesis, types of malignancy associated with DM/PM, and clinical implications of this data.

Association Between Malignancy and DM/PM

The first report suggesting an association between malignancy and DM was published in 1916.\textsuperscript{3} Since then, a large number of case series and case reports were described in the literature. However, the first case-control study confirming the association of DM/PM with malignancy was published years later in 1985.\textsuperscript{4} Subsequent population-based retrospective cohort studies have consistently confirmed an increased risk of malignancy in the setting of DM, though one relatively small study failed to show a statistically significant increased risk in patients with PM. Table 1 summarizes the data from these epidemiological studies.\textsuperscript{4-9}

Cancer diagnosis can precede, parallel, or follow DM/PM diagnosis. The risk of a diagnosis of cancer is highest during the first year after the diagnosis of myositis. This relationship suggests that DM/PM may develop as a paraneoplastic process. However, detection of malignancy may be influenced by more aggressive cancer screening after the discovery of DM/PM. A parallel between clinical course of DM/PM and malignancy has also been described among some patients. Disappearance of skin rash and muscle weakness after treatment of the cancer, as well as recurrence of symptoms with
recurrence of the cancer, has been described in many case reports.[10,11] However, the course of DM/PM does not always correspond to the course of the cancer as described in a study by Bonnetblanc et al.[12]

Pathogenesis

The mechanism by which DM/PM increases the risk of malignancy remains unclear. Nonetheless, the observation that DM/PM could be a paraneoplastic process has led to a widely accepted hypothesis of the “cross-over” model that explains the phenomena of myositis as a cross reaction between tumor cell and damaged muscle fiber. Casciola-Rosen et al. observed that myositis specific antigens (Mi-2, Jo-1 and DNA-PKcs), normally expressed at a very low level in mature muscle cell and other tissues, are over-expressed in regenerating muscle fibers of patient with DM/PM and in adenocarcinoma of the lung and breast. The authors propose that these over-expressed antigens in the tumor are recognized by the immune system resulting in production of specific lymphocytes. These lymphocytes, under normal circumstances, do not attack muscle fibers due to low antigen expression. However, following muscle damage and regeneration by any etiologies, these antigens are over-expressed, leading to recognition and self-attack of the specific lymphocytes. This attack, in turn, causes more damage and regeneration resulting in more antigens expression and, again, more recognition and self-attack. This vicious cycle continues and ultimately gives rise to the overt clinical symptom of myositis.[13]

Furthermore, this model is supported by another recent study that examined the rectus abdominis muscle of patients with newly diagnosed colorectal cancer who did not have any clinical evidence of myositis. The biopsy was obtained at the time of surgery before any treatment for their underlying malignancy. The authors found that this biopsied muscle had increased number of regenerative myofibers without any inflammatory cell infiltration, which is seen in DM/PM affected muscles. This observation provides evidence of subclinical cancer-induced muscle injury, which may be the initial source of myositis specific antigens.[14]

Type of Malignancy

The type of malignancy found in patients with DM/PM, generally reflect those found in age- and sex-matched populations. Breast, lung, and colorectal cancer were the three most common cancers from Western country cohorts,[15-17] whereas nasopharyngeal carcinoma, one of the most common cancers in southern China and Southeast Asia, was the most common associated cancer in Asian studies.[18] This finding further supports the role of DM/PM as a paraneoplastic process that can virtually happen with any kind of cancer.

Of note, a preponderance of ovarian cancer was observed in several studies of Caucasians. This finding may suggest a closer association between ovarian cancer and myositis, or might just reflect the challenges associated with making a diagnosis of ovarian cancer.[19]

Evaluation of Cancer

A careful history and physical examination (including gynecological exam) along with age-appropriate

| Study | Type of Study | Database | Number of Patients with DM | Number of Patients with PM | SIR (95% CI) | Male | Female |
|-------|---------------|----------|----------------------------|---------------------------|--------------|-------|--------|
| Manchul et al.[4] | Case-control | Wellesley hospital, Toronto, Canada | 31 | 40 | 4.49 (1.4-14.2) | 2.4 (1.6-3.6) | 3.4 (2.4-4.7) |
| Sigurbergsson et al.[5] | Retrospective cohort | National hospital discharge registry, Sweden | 392 | 396 | 6.5 (3.9-10) | 1.7 (1.1-2.4) |
| Airio et al.[6] | Retrospective cohort | National hospital discharge registry, Finland | 71 | 175 | 1.7 (1.1-2.4) | 0.5 (1.8) |
| Chow et al.[7] | Retrospective cohort | National hospital discharge registry, Denmark | 203 | 336 | 1.7 (1.1-2.4) | 0.5 (1.8) |
| Stockton et al.[8] | Retrospective cohort | National hospital discharge registry, Scotland | 286 | 419 | 1.7 (1.1-2.4) | 0.5 (1.8) |
| Buchbinder et al.[9] | Retrospective cohort | Muscle biopsy performed in Victoria, Australia | 85 | 321 | 6.2 (3.9-10.0) | 0.5 (1.8) |

Study by Manchul et al. reported only overall risk of patients with DM or PM. DM: Dermatomyositis; PM: Polymyositis; SIR: Standardized incidence ratios; CI: Confidence interval.
cancer screening should be offered to every patient with newly diagnosed DM/PM. However, whether more aggressive investigations, such as computerized tomography (CT) scan should be pursued, is a subject of debate as we do not have any prospective, randomized controlled trials available to answer this question. Most experts recommend conventional approach in average-risk patients. However, in patients with high risk features, including older age of onset, severe cutaneous disease (cutaneous necrosis, leukocytoclastic vasculitis), severe muscular disease (distal muscle weakness, dysphagia, respiratory muscle involvement), resistance to treatment and markedly elevated inflammatory markers, more aggressive screening strategies should be considered. Whole-body positron emission tomography (PET)/CT has a potential role as a “one-stop” cancer screening tool. A recent study found that the PET/CT had a comparable sensitivity and specificity to thoracic/abdominal CT, mammography, gynecologic examination, ultrasonography, and tumor marker analysis.

A novel antibody, anti-p155/140, which was later identified as autoantibody to human transcriptional intermediary factor 1-gamma (TIF1-γ), has a very promising role in the evaluation of risk of malignancy among patients with DM/PM. TIF1-γ plays a key role in regulating the transforming growth factor beta (TGF-β) signaling pathway, which is an essential for carcinogenesis in various types of cancer. In 2012, Trallero-Araguas et al. conducted a systematic review and meta-analysis on the clinical utility of anti-p155/140 and concluded that anti-p155/140 had a high negative predictive value (ranging from 89% to 100%) that a negative result reasonably excluded the presence of occult malignancy that the more aggressive strategy should not be undertaken.

Association with Uncommon Type of IIMs

The evidence of the link between IBM and amyopathic dermatomyositis (ADM) is not as robust as in DM and PM. Data on IBM are conflicting. For example, a population-based cohort study conducted by Buchbinder et al. found a significant increased risk of malignancy with Standardized incidence ratios (SIR) of 2.4 (1.2-4.9), but a more recent study failed to show a significant association with SIR of 1.4 (0.8-2.3). Data on ADM is even more scarce, as, in part, it is a relatively uncommon entity and its definition is still somewhat confusing. The best available evidence is a systematic review of case reports and case series that included 291 patients. From that systematic review, 14% of patients had an associated cancer, which was comparable with the incidence of cancer in DM/PM. However, this data needs to be carefully interpreted as a case of ADM with associated cancer might be more likely to get published.

Conclusion

The association between malignancy and DM/PM has been well established with several epidemiological studies. The type of cancer found in this group of patients generally reflects the type of cancer found in that population. The optimal cancer screening strategy in this group of patient is a subject of debate. Recent studies showed a promising role of anti-p155/140 to exclude the presence of occult malignancy with a high negative predictive value, while PET/CT scan emerges as an alternative screening method that has a comparable sensitivity and specificity to the conventional aggressive strategy.

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