Review paper

Reumatologia 2015; 53, 2: 101–105
DOI: 10.5114/reum.2015.51510

Polymyositis and dermatomyositis as a risk of developing cancer

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Abstract

Polymyositis (PM) is an idiopathic inflammatory myopathy that affects striated muscles. Dermatomyositis (DM) is an idiopathic inflammatory myopathy with presence of skin symptoms. Both are characterized by acute or subacute onset, symmetrical proximal muscle weakness, the presence of mononuclear cell infiltrates of the muscles and increased activity of muscle enzymes. The treatment still remains glucocorticoids and disease-modifying drugs. Symptoms of PM/DM can be a signal of developing cancer. Known risk factors for cancer in patients with PM/DM are older age, male gender, dysphagia, skin necrosis, cutaneous vasculitis, rapid onset of the disease, elevated creatinine kinase (CK) and C reactive protein (CRP), and an increase in the erythrocyte sedimentation rate (ESR). Recently three new myositis-specific autoantibodies (MSA) predicting the risk of cancer have been discovered: melanoma differentiation-associated protein 5 (anti-MDA-5), transcription intermediary factor 1γ (TIF-1γ), and nuclear matrix protein NXP-2.

Key words: myositis, cancer risk, paraneoplastic syndromes.

Introduction

Polymyositis (PM) and dermatomyositis (DM) are rare diseases. The incidence of PM/DM is 8/100,000, and it usually occurs in children between 5 and 15 years old and in adults between 40 and 60 years old. DM is more common than PM. The female to male ratio is 2 : 1. Pathogenesis still remains unclear. Some genetic factors such as the genes HLA-B8, DR3 and HLA-DRW52 may predispose to the development of PM/DM. Viral infections, especially Epstein-Barr and Coxsackie viruses, can trigger an autoimmune myositis by molecular mimicry with some muscle antigens. Polymyositis is a type of idiopathic inflammatory myopathy which usually affects striated muscles. DM is an idiopathic inflammatory myopathy with the presence of characteristic symptoms such as heliotrope rash around the eyes, neck shaped "V" erythema, shoulders and neck erythema in the form of a scarf, and erythema on the hips and thighs at the lateral surface (holster symptom). Other skin manifestations characteristic for DM include Gottron's sign as maculopapular lesions consisting of prominent red, scaly spots located on the extensor surfaces of interphalangeal and metacarpophalangeal and interphalangeal hand and joints, appearing also around the elbow and knee. Other changes are nail telangiectasia and ulcers due to cutaneous vasculitis most commonly located on the extremities. Inflammatory myopathies may be accompanied by usually non-erosive arthritis, calcification of soft tissue and skeletal muscle, especially in the region of elbows and knees. This symptom is most likely to occur in the form of child DM. Raynaud's phenomenon is present in 10–15% of patients. Both PM and DM are characterized by acute or subacute onset, symmetrical proximal muscle weakness, the presence of mononuclear cells that infiltrate in the histologic examination of muscle biopsies and increased muscle enzymes: creatine phosphokinase (CK), alanine aminotransferase (ALT), asparagines aminotransferase (AST) and lactate dehydrogenase (LDH) as a result of muscle damage.

An immunological marker for PM/DM is anti-Jo-1 antibody, and it has a high diagnostic specificity, but is present only in 30% of patients. The determination of presence in serum of anti-Jo-1 by qualitative ELISA is important for the

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Submitted: 19.03.2015; **Accepted:** 28.04.2015

diagnosis of PM. Jo-1 is an antibody to histidyl-RNA-synthetase and is a member of the myositis-specific antibodies (MSA) and the group of antibodies against aminoacyl-tRNA synthetases (ARS). Myositis-specific antibodies autoantibodies are shown in Table I.

Patients with ARS antibodies have a predilection to interstitial lung disease (ILD) and a worse prognosis than patients without lung involvement. The presence of anti-SRP (signal recognition particle) antibodies is combined with the risk of developing rhabdomyolysis and a worse response to steroids. Anti-Mi-2 antibodies are strongly correlated with DM. In the course of PM/DM changes in other systems such as the heart (arrhythmias) or gastrointestinal tract (motility disorders and particularly its weakness) are observed. The basis for the treatment of inflammatory myopathy is still high doses of glucocorticoids and, depending on the activity of inflammatory symptoms in organs, disease-modifying drugs such as methotrexate, azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, tacrolimus are in use. In severe cases the therapeutic options are infusions of immunoglobulins and plasmapheresis. Currently there are attempts to use new therapies and biologics, such as inhibitors of tumor necrosis factor (anti-TNF), rituximab (anti CD-20) and sifalimumab (human monoclonal antibody binding and neutralizing human IFN-α). Worse prognosis depends on organ involvement (ILD, dysphagia), older age, delayed steroid treatment and development of cancer. Polymyositis and DM symptoms can be a sign of existing cancer or may also increase the risk of malignancy. The most common cancers described in cancer associated dermatomyositis (CADM) are: breast cancer, lung, ovary, stomach, intestine, nasal cavity, throat, pancreatic, bladder and Hodgkin's lymphoma [1–3].

The risk of cancer in polymyositis and dermatomyositis

Both DM and PM increase the likelihood of developing cancer (6-fold and 2-fold respectively). The diagnosis of cancer may precede, coincide with or follow the diagnosis of DM/PM. The greatest risk exists in the first year after the diagnosis of polymyositis, which suggests that DM/PM can develop as a paraneoplastic process. The type of cancer that often occurs in patients with DM/PM reflects the characteristics such as origin, age and gender. Tumors of the breast, lung and colorectal cancer are diagnosed as the three most common in patients in Western civilization, and nasopharyngeal cancer is one of the most common cancers in southern China and Southeast Asia. However, every type of cancer can cause paraneoplastic syndrome as DM/PM. It has been proved that polymyositis is strongly associated with certain types of malignant lymphomas, especially Hodgkin lymphoma [1].

Table I. Myositis-specific antibodies, acc. to [17]

Myositis-specific antibodies		Autoantibody frequency
Anti-synthetase antibodies		30–40%
Anti-Jo-1	anti-histidyl-tRNA synthetase	most common (about 20% of idiopathic inflammatory myopathies)
PL 12	anti-alanyl-tRNA synthetase	
PL 7	anti-threonyl-tRNA synthetase	
EJ	anti-glycyl-tRNA synthetase	
OJ	anti-isoleucyl-tRNA synthetase	
KS	anti-asparaginyl-tRNA synthetase	
Zo	anti-phenylalanyl-tRNA synthetase	
Ha	anti-tyrosyl-tRNA synthetase	
Mi-2 (anti-nuclear ATPase/helicase)		< 10%
SRP signal recognition particle – anti-ribonucleoprotein (proteins 7SLRNA)		5%
Anti-TIF1-γ (anti-p155/140 autoantibodies)		13–21%
Anti-MDA-5 (cytoplasmic protein melanoma differentiation-associated gene 5		unknown
NXP-2 (nuclear matrix protein)		unknown
Anti-SAE (anti-small ubiquitin-like modifier activating enzyme)		5%

A rare non-Hodgkin's lymphoma is a peripheral T cell lymphoma, with poor prognosis and frequent relapses. A common metabolic complication of cancer is hypercalcemia – the serum calcium levels may be above 3.5 mmol/l, which may result in a hypercalcemic crisis [1]. The main cause of hypercalcemia is an increase in bone resorption, and, in some cases, multiple myeloma and other lymphoproliferative diseases. The most common symptoms of hypercalcemia are: headache, drowsiness, coma, tendon hyperreflexia, temporarily paralyzing facial muscles, tachycardia and hypertension, and muscle weakness, which may, in patients with DM/PM, be difficult to determine in advance. In patients treated with digitalis, hypercalcemia occurs in the case of hypersensitivity to these drugs. Other symptoms of hypercalcemia are polyuria, calcinosis and nephrolithiasis, nausea, vomiting, constipation, loss of appetite, inflammation of the pancreas and biliary lithiasis. As mentioned above, some signs of DM/PM can mask hypercalcemia, so patients should monitor the levels of calcium by weakening of muscles or severity of gastrointestinal symptoms despite effective treatment used previously. The occurrence of hypercalcemia in patients with PM/DM can also draw attention to the need for further evaluation of the cancer. A feature observed in adults with DM is an increased incidence of lung cancer [2]. The frequency of lung cancer in patients with DM is higher in the elderly than in younger patients. The study of de Souza and Shinjo [3] showed that from a group of patients with cancer 8.6% also had an established diagnosis of DM. The authors pointed out that women were more often diagnosed with cancers. The opposite observation in patients with DM was presented by Zhang [4]. Hill et al. [5] reported in a population-based study 618 patients with dermatomyositis, of whom 198 had cancer. From this group 115 patients developed cancer after the diagnosis of dermatomyositis. Polymyositis was diagnosed in 914 patients, of whom 137 had cancers. In 95 cases of PM the cancer diagnosis was established after the diagnosis of PM. The authors concluded that DM is strongly associated with malignant diseases and PM increases the risk of cancers [5].

Surgical treatment in patients with DM and lung cancer in some cases may significantly reduce symptoms of DM and may lead to recovery from DM also in patients previously resistant to pharmacological treatment [6]. Endometrial cancer is the most common cancer of the reproductive organs in the United States; there are about 40,000 new cases per year [7].

Risk factors include older age, diabetes, and conditions with increased levels of estrogen: obesity, early menarche, late menopause, polycystic ovarian syndrome. The most common symptom of endometrial cancer is bleeding after menopause. The first case of stomach cancer associated with symptoms of DM was presented in 1916 by Stertz [8]. Since then, numerous case reports have shown that they are much more common in women over 50 years of age in conjunction with cancer of the ovary, lung, pancreas, stomach and colon, and lymphomas. However, ovarian cancer appears to be most closely connected with dermatomyositis, and the relationship of other cancers of the reproductive organ with PM and DM is relatively weak. Bladder cancer (transitional cell carcinoma – TCC) may be associated with various paraneoplastic syndromes manifesting as endocrine, neuromuscular, or hematological disorders, and paraneoplastic DM secondary to cancer of the bladder TCC is rarely observed [9]. The symptoms of DM appear extremely rarely when signs of metastatic TCC are observed. Cutaneous malignant tumors are also often associated with autoimmune connective tissue diseases, including PM/DM [10]. The relationship between systemic connective tissue diseases and the development of skin cancer is based on disorders of the immune system, inflammation, application of immunosuppression and increased susceptibility to viral infections. Additional causes include environmental factors such as UV radiation and smoking.

The pathogenesis of development of malignancy in PM/DM is poorly understood, but it is believed that it is caused by altered cellular and humoral immunity. Myositis-specific autoantigens – histidyl-t-RNA (HRS/Jo-1) – are expressed within the muscles undergoing regeneration (in muscle cells), lung cancer cells, breast cancer, and hepatocellular carcinoma, which suggests that cross-reaction against self-antigens of cancer cells and muscle cells may occur [11, 12].

Assessment of risk of developing cancer

In view of the increased risk of confirmed cancers in patients with DM/PM, there is a question of the risk assessment of individual patients. It is known that some patients with DM (10–20%) have an increased risk of cancer at the time of diagnosis of DM. The identification of patients at high risk of cancer remains a priority in the diagnosis and treatment of these patients. Even in about 1/3 of patients with DM the malignant process may occur in three years [13].

The cancer risk factors in patients with PM/DM under consideration are: age over 60, male gender, dysphagia, skin necrosis, cutaneous vasculitis, rapid onset (< 4 weeks), elevated CK, an increase in the ESR and a high level of C-reactive protein. Additionally, the co-occurrence of diabetes with the above risk factors in patients with PM/DM increases the risk of cancer development. On the other hand, the presence of interstitial

lung disease, arthritis, Raynaud's syndrome, or anti-Jo-1 antibody indicates less than average risk of developing cancer. The presence of antibodies to extractable nuclear antigens (anti-ENA) seems to be associated with reduced risk of cancer. Recently three new DM-specific autoantibodies, which may be important in predicting the risk of developing cancer, have been discovered: melanoma differentiation-associated protein 5 (anti-MDA-5), transcription intermediary factor 1γ (TIF-1γ), and nuclear matrix proteins NXP-2 (also known as MORC3) [14]. Fujimoto and colleagues [15] confirmed earlier the observations that anti-155/140 kD may be important cancer markers – these antibodies are directed against transcription intermediary factor-1α (TIF-1α) and, to a lesser extent, TIF-1β and TIF-1γ. All these antigens are characterized by similar resolution in sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). Studies have shown that antibodies against TIF-1γ and NXP-2 are very common in DM; they were present in 55% of patients with DM (17% for anti-NXP-2 and 38% for anti-TIF-1γ) [16]. Anti-NXP-2 and anti-TIF-1γ antibodies significantly often occur in cases of CADM. In observations by Fujimoto et al. [15], 29 patients had CADM, in 15 patients anti-TIF-1γ antibodies were found and in 9 anti-NXP-2 antibodies were found. The authors suggested that the absence of anti-TIF-1γ and NXP-2 antibodies protects against cancer. Additionally, some of the patients with these antibodies had antibodies to other antigens specific for DM, such as MI-2, SAE1/2 (SUMO1 activating enzyme subunit 1), MDA-5, and t-RNA synthetases. It has been shown that there is a strong link between NXP-2 antibodies and the risk of developing cancer, often unexpectedly associated with male gender, but the reason for this association is not clear. The dependence of cancer risk and older age of the patients with DM is known, and recent studies show that there is a relationship between the incidence of cancer and age ≥ 60 and the presence or absence of anti-NXP-2 and anti-TIF-1γ. In patients of over 60 years of age with no anti-TIF-1γ or anti-NXP-2 the incidence of cancer is very low (2.6%), and it is higher (11%) in patients under 60 who have anti-TIF-1γ or anti-NXP-2 autoantibodies. Cancer was detected in six out of eleven patients older than 60 years and having anti-NXP-2 [17–19].

New antibodies, identified as autoantibodies to human factor 1γ intermediary transcription (anti-TIF-1γ), may be a promising marker in the assessment of cancer risk in patients with DM/PM [15]. In 2012 Trallero-Araguas et al. [19] conducted a study on the clinical utility of anti-P155/140 antibodies, and found that they have a high negative predictive value (ranging from 89% to 100%), so a negative result is likely to exclude the presence of cancer. It has been shown that TIF1 family proteins act synergistically to inhibit tumor growth in human and mouse models. TIF1β is overexpressed in various types of cancer tissues and is associated with the progression and metastasis of cancer. A clinical phenomenon of resistance in the development of muscle tissue metastases is also known. Several mediators released by the muscle cells may be responsible for rare metastatic tumor formation in that tissue. These cytokines possess anti-tumor activity, such as TNF-α, TGF (tumor growth factor), factor infiltrating lymphocytes, interferon-γ (IF-γ), lactic acid, and proteolytic enzymes such as plasminogen activator inhibitor.

In the course of DM, especially in the amyopathic form of this disease (ADM), rapidly progressive intestinal lung disease (ILD), which is a life-threatening condition, may develop. In this group of patients anti-MDA5 antibodies may help to better define this population. Additionally, these antibodies facilitate early diagnosis, determine prognosis and ultimately enable the development of randomized clinical trials to establish the optimal treatment for anti-MDA5-positive patients with a poor prognosis [20, 21]. Furthermore, as recently described, the measurement of anti-MDA5 also seems to be useful for monitoring the disease activity.

Summary

Careful medical history and physical examination of the patients (including gynecological examination), taking into account the patient's age and other risk factors described above, should be carried out and considered in any patient with suspected DM/PM. When the diagnosis of PM/DM is established, the estimation of cancer risk is necessary and further diagnostics are indispensable. It is debatable whether more accurate tests, such as computed tomography (CT), should be routinely used. Most experts recommend a conventional diagnostic approach to medium risk patients. In patients at high risk, including patients who are elderly at the time of onset, the presence of severe disease of the skin (skin necrosis, vasculitis), symptoms of severe myopathy (distal muscle weakness, dysphagia, respiratory muscle involvement), resistance to conventional treatment of DM/PM and significantly elevated markers of inflammation, more advanced screening should be considered. Positron emission tomography (PET) can act as a screening tool for cancer [22]. Recent studies have shown that PET/CT had comparable sensitivity and specificity for CT of the chest and abdomen, pelvic examination, mammography, ultrasound and analysis of tumor markers.

Despite the knowledge on the association of DM/PM with the occurrence of tumors, there is still a lack of

quick diagnosis and possibilities for carrying out further diagnostic tests in daily practice. New immunological markers are promising but require further studies.

The authors declare no conflict of interest.

References

1. Ding L, Xiao X, Huang L. Peripheral T-cell lymphoma with hypercalcemic crisis as a primary symptom accompanied by polymyositis: A case report and review of the literature. Oncol Lett 2015; 9: 231-234.
2. Przybylski G, Jarzemska A, Czerniak J, et al. A case report of a patient with dermatomyositis as a prodromal sign of lung cancer. Pol Arch Med Wewn 2008; 118: 143-147.
3. de Souza FH, Shinjo SK. Newly diagnosed dermatomyositis in the elderly as predictor of malignancy. Rev Bras Reumatol 2012; 52: 713-721.
4. Zhang W, Jiang SP, Huang L. Dermatomyositis and malignancy: a retrospective study of 115 cases. Eur Rev Med Pharmacol Sci 2009; 13: 77-80.
5. 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.
6. Shen Ch, Che G. Dermatomyositis as an antecedent sign of lung cancer in an elderly patient: a case report. J Thorac Dis 2014; 6: E15-E18.
7. Wada C, Hua CN, Carney ME. Paraneoplastic syndrome in Hawai'i: a case of dermatomyositis associated with endometrial cancer. Hawaii J Med Public Health 2014; 73: 112-114.
8. Stertz G. Polymyositis. Berl Klin Wochenschr 1916; 53: 489.
9. Fitzpatrick J, Wallace WA, Lang S, et al. Recurrent dermatomyositis manifesting as a sign of recurrent transitional cell carcinoma of urinary bladder: Long-term survival. Urol Ann 2014; 6: 264-266.
10. Kostaki D, Antonini A, Peris K, et al. Skin cancer risk in autoimmune connective tissue diseases. G Ital Dermatol Venereol 2014; 149: 567-580.
11. Soejima M, Kang EH, Gu X, et al. Role of innate immunity in a murine model of histidyl-transfer RNA synthetase (Jo-1)-mediated myositis. Arthritis Rheum 2011; 63: 479-487.
12. Howard OM, Dong HF, Yang D, et al. Histidyl-tRNA synthetase and asparaginyl-tRNA synthetase, autoantigens in myositis, activate chemokine receptors on T lymphocytes and immature dendritic cells. J Exp Med 2002; 196: 781-791.
13. Ungprasert P, Bethina NK, Jones CH. Malignancy and Idiopathic Inflammatory Myopathies. N Am J Med Sci 2013; 5: 569-572.
14. Fiorentino DF, Chung LS, Christopher-Stine L, et al. Most Patients With Cancer-Associated Dermatomyositis Have Antibodies to Nuclear Matrix Protein NXP-2 or Transcription Intermediary Factor 1γ*. Arthritis Rheum 2013; 65: 2954-2962.
15. Fujimoto M, Hamaguchi Y, Kaji K, et al. Myositis-specific anti-155/140 autoantibodies target transcription intermediary factor 1 family proteins. Arthritis Rheum 2012; 64: 513-522.
16. Hoshino K, Muro Y, Sugiura K, et al. Anti-MDA5 and anti-TIF1-γ antibodies have clinical significance for patients with dermatomyositis. Rheumatology 2010; 49: 1726-1733.
17. Gunawardena H, Betteridge ZE, McHugh NJ. Myositis-specific autoantibodies: their clinical and pathogenic significance in disease expression. Rheumatology 2009; 48: 607-612.
18. Lu X, Yang H, Shu X, et al. Factors predicting malignancy in patients with polymyositis and dermatomyostis: a systematic review and meta-analysis. PLoS One 2014; 9: e94128.
19. Trallero-Araguás E, Rodrigo-Pendás JÁ, Selva-O'Callaghan A, et al. Usefulness of anti-p155 autoantibody for diagnosing cancer-associated dermatomyositis: a systematic review and meta-analysis. Arthritis Rheum 2012; 64: 523-532.
20. Fujisawa T, Hozumi H, Kono M, Enomoto N. Prognostic factors for myositis-associated interstitial lung disease. PLoS One 2014; 9: e98824.
21. Sato S, Hoshino K, Satoh T, et al. RNA helicase encoded by melanoma differentiation-associated gene 5 is a major autoantigen in patients with clinically amyopathic dermatomyositis: Association with rapidly progressive interstitial lung disease. Arthritis Rheum 2009; 60: 2193-2200.
22. Gallamini A, Zwarthoed C, Borra A. Positron emission tomography (PET) in oncology. Cancers (Basel) 2014; 6: 1821-1889.