Ref: Ro J Rheumatol. 2022;31(4)
DOI: 10.37897/RJR.2022.4.4

"Playing detective" in a case of paraneoplastic polymyositis

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ABSTRACT

Adult-onset polymyositis (PM) belongs to the idiopathic inflammatory myopathy (IIM) group and manifests with proximal muscle weakness, elevated muscle enzymes and positive myositis- specific antibodies. The subset of autoantibodies can indicate a higher risk for cancer association. An 82-year-old diabetic patient, with multiple cardio-vascular comorbidities, was hospitalized for muscle weakness of the upper girdle, dysphagia and dysphonia, accompanied by elevated serum muscle enzymes. Muscle biopsy showed an inflammatory infiltrate while immunological assays found positive ANA and anti-NXP2 antibodies. The diagnosis of PM was established, thus a screening for underlying neoplasia was required. Upper endoscopy visualized an area of ectopic mucosa in the esophagogastric junction and the biopsy confirmed a squamous cell carcinoma in situ. Patient had favorable muscle outcome under methylprednisolone pulse therapy. It is worth noting that polymyositis is more rarely associated with cancers as compared to dermatomyositis (DM). In conclusion, the type of antibodies identified in myositis can represent an alarm signal for oncologic screening, making possible an early diagnosis and efficient treatment of a hidden tumor.

Keywords: polymyositis, idiopathic inflammatory myopathy, skeletal muscles, autoantibodies

INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are a group of systemic conditions mainly targeting skeletal muscles but also skin, joints and other organs. IIM are characterized by proximal symmetric muscle weakness and elevated serum muscle enzyme levels. Depending on the presence of specific autoantibodies, clinical phenotype may differ, thus their detection being useful in both diagnosis and disease outcome [1].

Polymyositis (PM), a subtype of IIM, can be associated with an increased risk of underlying cancer in patients aged over 40 years. There have been numerous documented risk factors, such as older age at disease onset, dysphagia, diabetes or the presence of antibodies to transcription intermediary factor (TIF)-1 gamma or antibodies to nuclear matrix protein (NXP)-2 (anti-MJ or anti-p140). Conversely, the presence of myositis-specific (anti-synthetase antibodies, anti-Mi-2, anti-SRP, anti-MDA5) and myositis-associated antibodies (anti-RNP, anti-PM-Scl, anti-Ku) has been reported to associate a lesser risk of malignancy [2].

CASE REPORT

An 82-year-old male patient was transferred from an emergency hospital to the Rheumatology department, after presenting with severe symmetrical muscle weakness affecting the upper girdle (Figure 1) with progressive onset over the last month. Dysphagia and dysphonia were simultaneously associated. He had a history of type-2 diabetes and multiple cardiovascular conditions, namely arterial hypertension, permanent atrial fibrillation, metallic mitral prosthesis, tricuspid annuloplasty and a coronary artery bypass. He was undergoing treatment with acenocoumarin, low-dose acetylsalicylic acid, diuretics, beta-blocker, statin and metformin.

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Article History:
Received: 26 December 2022
Accepted: 30 December 2022

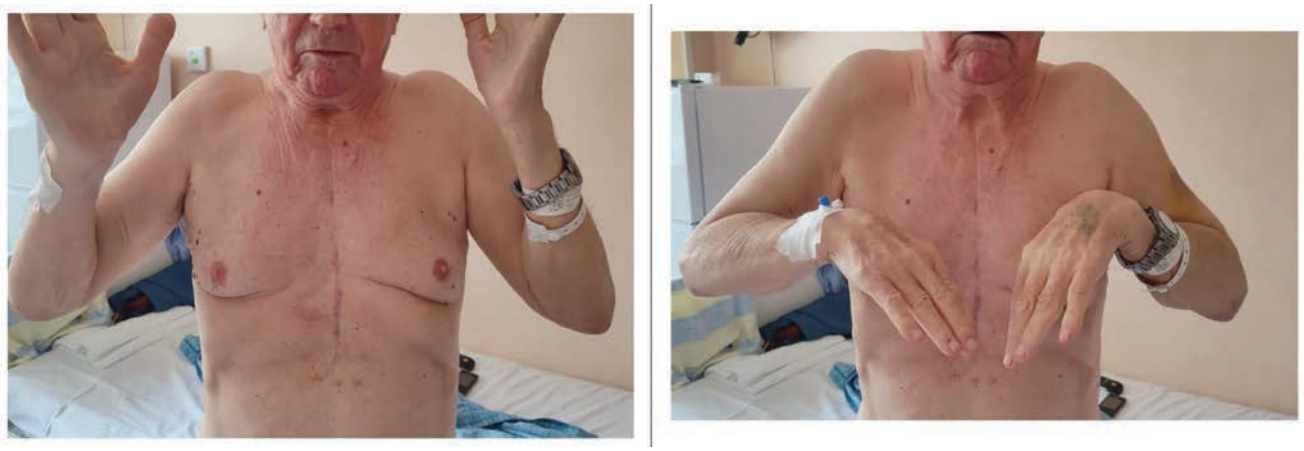

FIGURE 1. Symmetrical muscle weakness and limited abduction of the upper limbs

Initial assessment ruled out myasthenia gravis since no palpebral ptosis was present. A cerebral magnetic resonance imaging (MRI) excluded the presence of intracranial mass, while an extensive computed tomography (CT) scan found no abnormal features in the thorax, upper abdomen or pelvis. The patient's thyroid function was normal. However, the biological setting indicated a significant rhabdomyolysis syndrome (creatine kinase 3,999 U/l, lactate dehydrogenase LDH 502 U/L, aspartate aminotransferase ASAT 156 U/l) and increased inflammation (C-reactive protein CRP 14.11 mg/l, fibrinogen 533 mg/dl). Thus, the patient was referred to Rheumatology, after receiving five days of intravenous dexamethasone.

Upon admission in our hospital, the patient had significant muscle weakness of the upper limbs, dysphonia and dysphagia. However, no Raynaud's or cuticular overgrowth and no rashes were present. The inflammatory syndrome had already decreased, as well as the muscle enzyme levels (CK 556 U/L).

Taking into account the clinical presentation, the rapid onset and the marked muscle enzyme increase, an idiopathic inflammatory myopathy was considered. Nevertheless, an accurate diagnosis included ruling out a number of other possible diseases. Among them, statin-induced myopathy and Trichinella infectious myositis were assessed, but test results came back negative.

Viral hepatitis was also excluded and so were electrolyte disorders for which normal serum calcium and potassium levels argued against.

Further investigations were mandatory to confirm diagnosis. Consequently, oral anticoagulants were replaced with parenteral heparin in order to perform a muscle biopsy from the affected deltoid. The latter indicated muscle oedema, perifascicular atrophy, rare inflammatory elements in the interstitium, suggestive of inflammatory myopathy. Shoulder ultrasound described a subacromial bursitis and deltoid atrophy (Figure 2). Antinuclear antibodies (ANA) in immunofluorescence assay were 1/320 and anti NXP2 antibodies were strongly positive, while the rest of the extended myositis panel was negative.

Once the muscle biopsy was completed (Figure 3), pulse therapy of methylprednisolone was started, with close monitoring of blood pressure and glycemia. The evolution was promptly favorable, with significant improvement of the muscle symptoms and decreasing levels of muscle enzymes.

Considering the clinical manifestations, the laboratory and immunological tests and biopsy results, the diagnosis of adult-onset idiopathic polymyositis

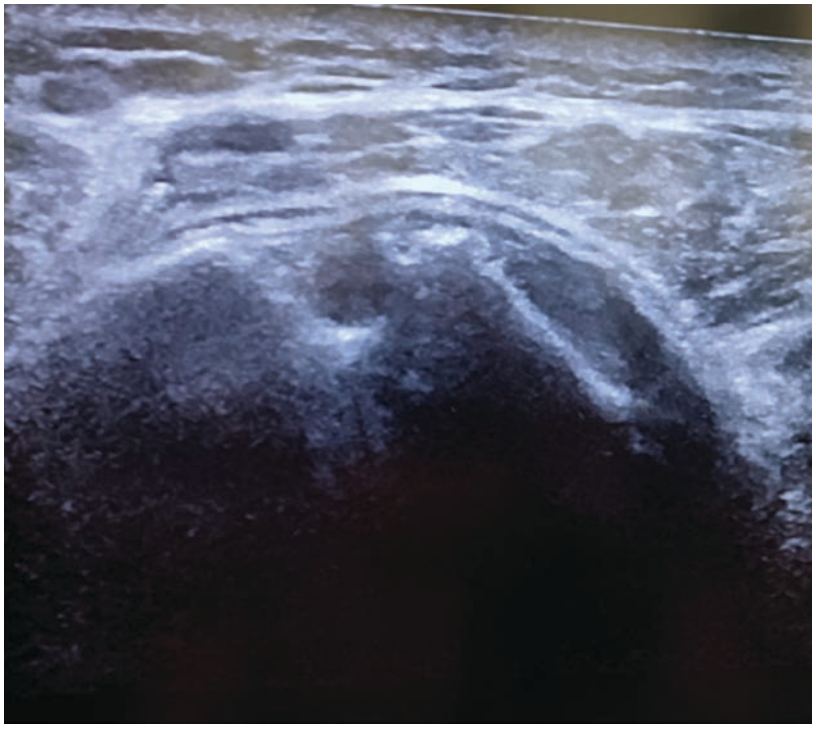

FIGURE 2. Symmetrical muscle weakness and limited abduction of the upper limbs

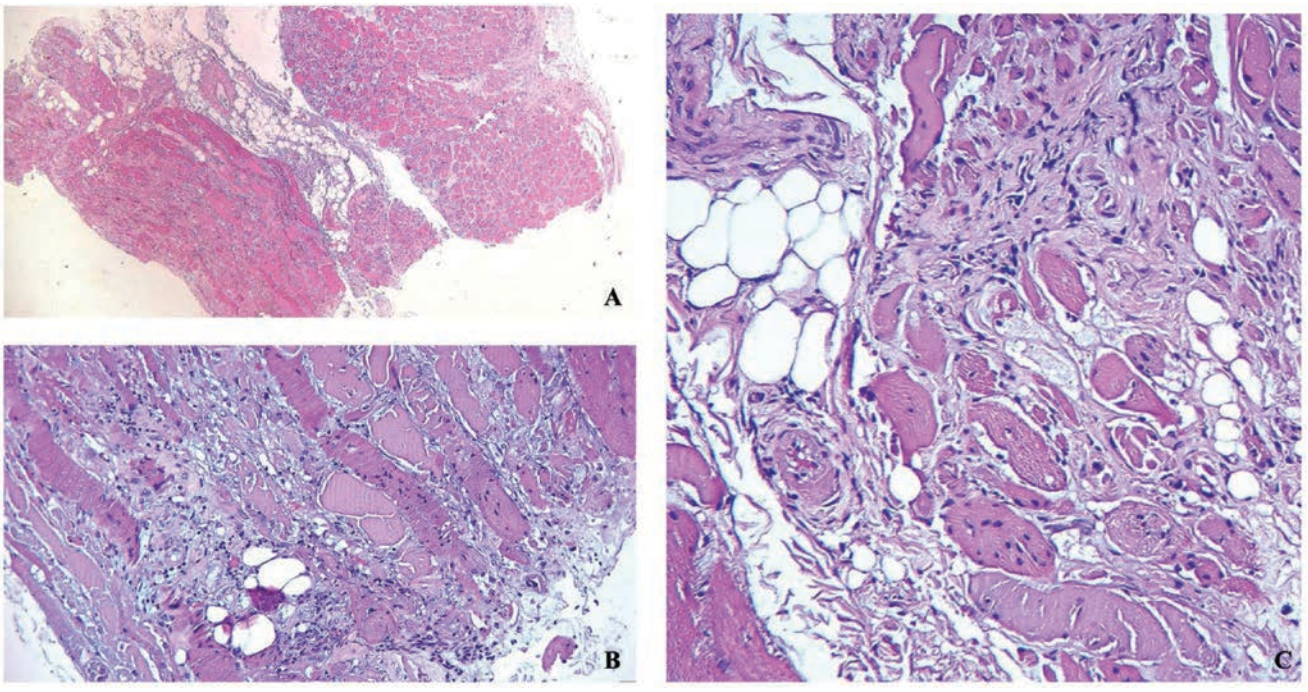

FIGURE 3. Histopathological aspect of muscle biopsy (A. Myositis HE 5x; B. interstitial lymphoplasmacytic inflammation HE 10x; C. atrophic muscle fibres HE 10x)

(PM) was established, according to the Bohan and Peter classification criteria [3].

Bearing in mind that associated cancers are present in about 10-20% of adult patients with PM and even in a higher percentage for the patients older than 65, a screening for underlying neoplasia was imposed [4]. Tumoral markers, ENT examination were negative for any abnormalities. The patient refused to undergo a colonoscopy. Nevertheless, the barium swallow test was performed and showed a lag in the deglutition process and unregulated contouring of the inferior thoracic oesophagus. Further testing included upper endoscopy which described ectopic gastric mucosa in the lower oesophagus. The suspicious site biopsy confirmed an ulcerated nonkeratinizing squamous cell carcinoma in situ staged TxN0M0 as in Figure 4.

The patient was discharged with significant muscle strength recovery and minimally increased muscle enzymes. He was prescribed oral methylprednisolone until reassessment and was referred to Oncology in order to establish the most suitable therapeutic approach.

DISCUSSIONS

The anti-NXP2 antibodies (anti-MJ antibodies) regulate RNA metabolism and transcription and can be present in up to a quarter of juvenile DM, usually associated with severe muscle atrophy and functional impairment [5]. In contrast, the clinical phenotype associated with anti NXP2 antibodies in adults is more likely to consist of severe muscle weakness, peripheral oedema, calcinosis and significant dysphagia. Of note, our patient experienced these muscular symptoms, yet he lacked peripheral oedema and calcinosis.

In adults this subtype is strongly associated with malignancy, since NXP2 is also a key factor in the activation of the p53 tumoral suppressor gene [6].

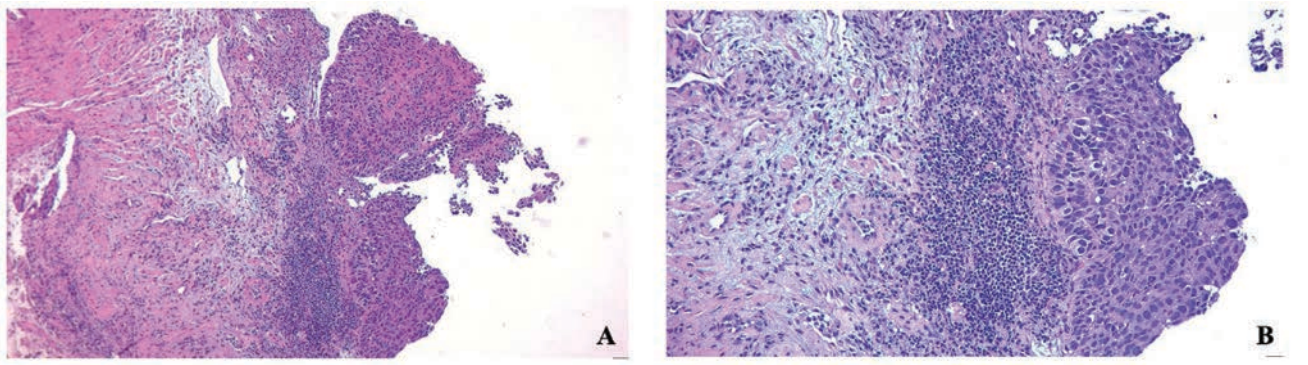

FIGURE 4. Histopathological confirmation of esophageal in situ squamous carcinoma (A. HE 5x, B. HE 10x)

Age-appropriate screening may be insufficient in detecting underlying malignancy, especially when the patient does not experience additional symptoms [3]. In the presented case, the diagnosis was rapidly set since the patient experienced dysphagia leading to a symptom-targeted screening.

Another particularity of this case originates from the fact that the cancer rates reported with PM are consistently lower than that of DM [7]. Even in such a case, adenocarcinomas of the cervix, lung, ovaries, pancreas, bladder and stomach account for approximately 70% of the cancers associated with IIM [8]. Squamous cell carcinoma is rarely reported [8].

There are a number of risk factors that are incriminated as risk for malignancy. Among them, older age, dysphagia, cutaneous necrosis or leukocytoclastic vasculitis need to be mentioned. Nevertheless, it is arguable whether dysphagia in our case is caused by reduced pharyngeal contractility of the throat or it was a direct consequence of the upper oesophageal sphincter obstruction. Specific paraneoplastic immune-mediated mechanisms might also contribute to dysfunction of swallowing. Most case reports of NXP-2 DM/PM complicated by dysphagia were refractory to systemic corticosteroid treatments and required additional treatments such as immunosuppressants and intravenous immunoglobulins. However, the patient showed favorable responses to high dose methylprednisolone.

CONCLUSIONS

PM represents a serious and often challenging to treat condition. Different subsets of antibodies are important in the initial clinical evaluation and anticipating patient prognosis. Anti-NXP2 antibodies indicate a poorer prognosis, since they predict a higher risk of simultaneous malignancy. PM can be a hallmark of an underlying asymptomatic disease, so regular screening is recommended in these cases, even in the following years after diagnosis. Meta-analyses showed that the majority of cancers are detected within five years before and after the diagnosis of IIM. As a result, cancers can be discovered early so that appropriate management can be applied.

Conflict of interest: none declared
Financial support: none declared

REFERENCES

1. Ceribelli A, Fredi M, Taraborelli M et al. Anti-MJ/NXP-2 antibodies are the most common specifcity in a cohort of adult caucasian patients with dermatomyositis. *Annals of the Rheumatic Diseases* 2012;71:A49.
2. Leatham H, Schadt C, Chisolm S, Fretwell D, Chung L, Callen JP et al. Evidence supports blind screening for internal malignancy in dermatomyositis: Data from 2 large US dermatology cohorts. *Medicine* (Baltimore). 2018 Jan;97(2):e9639. doi: 10.1097/MD.0000000000009639. PMID: 29480875; PMCID: PMC5943873.
3. Fiorentino DF, Chung LS, Christopher-Stine L, Zaba L, Li S, Mammen AL et al. Most patients with cancer-associated dermatomyositis have antibodies to nuclear matrix protein NXP-2 or transcription intermediary factor 1γ. *Arthritis Rheum.* 2013 Nov;65(11):2954-62. doi: 10.1002/art.38093. PMID: 24037894; PMCID: PMC4073292.
4. Jakubaszek M, Kwiatkowska B, Mälińska M. Polymyositis and dermatomyositis as a risk of developing cancer. *Reumatol*. 2015;53(2):101. PMICD: PMC4847280
5. Wang X, Ding Y, Zhou Z, Hou J, Xu Y, Li J. Clinical characteristics and poor predictors of anti-NXP2 antibody-associated Chinese JDM children. *Ped Rheumat.* 2021 Dec 1;19(1):1–9.
6. Hu T, Vinik O. Dermatomyositis and malignancy. Canadian Family Physician [Internet]. 2019 Jun 1;65(6):409. PMCID: PMC6738379/
7. Hill CL, Zhang Y, Sigurgeirsson B, Pukkala E, Mellemkjaer L, Airio A et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. *Lancet*. 2001 Jan 13;357(9250):96–100.
8. Gabrilovich M, Raza M, Dolan S, Raza T. Paraneoplastic Polymyositis Associated With Squamous Cell Carcinoma of the Lung. *Chest*. 2006 Jun 1;129(6):1721–3.