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Case Report

Rare Association of Dermatomyositis with Mixed Adenoneuroendocrine Carcinoma (MANEC) of the Gallbladder

Gabriela Puziski Ferreira de Melo¹, Marcelo Magalhães da Silveira Neto²,
Mariana Pires de Sá Valeriano³, Vanessa Miranda Pereira Fausto⁴,
Rafaella Lima Borges de Mendonça⁵ and Lucas José Sá da Fonseca^{6*}

¹Medical Resident of Dermatology, Hospital Universitário Professor Alberto Antunes, Federal University of Alagoas, Maceió, Alagoas, Brazil.

²Medical Resident of Pathology, Hospital Universitário Professor Alberto Antunes, Federal University of Alagoas, Maceió, Alagoas, Brazil.

³Medical Doctor (Dermatologist), Hospital Universitário Professor Alberto Antunes, Federal University of Alagoas, Maceió, Alagoas, Brazil.

⁴Medical Doctor (Rheumatologist), Hospital Universitário Professor Alberto Antunes, Federal University of Alagoas, Maceió, Alagoas, Brazil.

⁵Medical Doctor (Pathologist), Hospital Universitário Professor Alberto Antunes, Federal University of Alagoas, Maceió, Alagoas, Brazil.

⁶Medical Resident of Rheumatology, Hospital Universitário Professor Alberto Antunes, Federal University of Alagoas, Maceió, Alagoas, Brazil

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Dermatomyositis is an inflammatory myopathy of not fully understood etiology that may be associated with neoplasms. Representing a systemic autoimmune disease, the hallmarks of its clinical presentation are seen as cutaneous and skeletal muscle manifestations. The main cutaneous signs are represented by heliotrope and the Gottron's papules, while the muscular compromise is observed by proximal weakness and dysphagia. Diagnosis relies upon clinical history, physical examination and laboratory tests, and the first-line treatment is based on the use of systemic corticosteroid. The present manuscript reports a case of paraneoplastic dermatomyositis secondary to mixed adenoneuroendocrine carcinoma, an extremely rare association. Considering the potential aggressiveness of such tumor, the screening of occult neoplasms in dermatomyositis should also include the gallbladder assessment, aiming the early diagnosis and prompt specific treatment. Physicians must be aware of such possible association, once early diagnosis positively impacts in prognosis.

Keywords: Dermatomyositis, gallbladder, paraneoplastic, mixed adenoneuroendocrine carcinoma.

List of Abbreviations

MANEC; mixed adenoneuroendocrine carcinoma.

INTRODUCTION

Dermatomyositis is an inflammatory myopathy which may affect both children and adults (Dalakas, 2015), being more common in women (McGrath et al., 2018). Despite

the fact that, to date, its etiology is not fully understood, the association of such autoimmune myopathy with neoplasms is well acknowledged (Dalakas, 2015; McGrath et al., 2018), and malignancies may present themselves before, concomitantly or after the clinical manifestations of dermatomyositis (Jurcic, 2015). In this regard, the gallbladder is not a frequent site of neoplasm in paraneoplastic dermatomyositis, with only six case

*Corresponding Author E-mail: lucasjsdf@hotmail.com;
Phone: +55 82 3202-3935



Figure 1. (A) Erythematous-violet scaly plaques with areas of hypochromia in the extensor face of the left upper limb. (B) Erythematous-violet scaly plaques with areas of hypochromia in the upper trunk (V-neck sign).

reports found in the PubMed database until December 2018. Indeed, less than 5% of gallbladder tumors are represented by neuroendocrine carcinoma (Acosta et al., 2015), being adenocarcinoma the most common type of neoplasm (Mondolfi et al., 2011; Kamboj et al., 2015). The mixed adenoneuroendocrine carcinoma (MANEC), in turn, is a rare entity (Mondolfi et al., 2011; Song et al., 2012) that may derive from any part of the digestive tract as long as its origin comes from embryonic gut (Acosta et al., 2015), being formed by a composite of adenocarcinoma cells with areas of neuroendocrine carcinoma cells (Meguro et al., 2014; Kamboj et al., 2015).

Circulating autoantibodies are identified only in approximately 25% of patients with dermatomyositis, with anti-Jo-1 being the most frequently found. Cutaneous manifestations are variable, with the most common represented by the heliotropic erythema with palpebral and periorbital swelling. Muscle impairment is characterized by proximal weakness and dysphagia, and skin lesions may precede muscle compromise (Junior et al., 2014; Dalakas, 2015). The diagnosis is made mainly through clinical manifestations, physical examination and laboratory tests (creatinine phosphokinase, CPK; aldolase, and autoantibodies), as well as muscle biopsy and electromyography (Dalakas, 2015; McGrath et al., 2018). The first-line treatment is made with systemic corticosteroid, which may or may not be associated with corticosteroid-sparing immunosuppressive drugs such as methotrexate, azathioprine, tacrolimus, intravenous immune globulin, cyclosporine, mycophenolate, cyclophosphamide and rituximab (Dalakas, 2015; Sasaki et al., 2018). When it comes to paraneoplastic dermatomyositis, treating the associated malignancy may improve cutaneous signs and myopathic symptoms (McGrath et al., 2018).

CASE PRESENTATION

A 52-year-old female patient sought outpatient care because of pruritic lesions in the body and periorbital swelling for approximately 5 months, besides muscle weakness in the last 2 months. The dermatological examination revealed erythematous and scaly plaques with some areas of hypochromia in the extensor face of the upper limbs (Figure 1A), upper chest (Figure 1B), periumbilical area (Figure 2A), flanks, proximal third of the thighs, gluteus (Figure 2B) and right knee (Figure 3B), as well as edema and erythema in the periorbital region, mainly on the right side (Figure 3A).

Diagnostic hypotheses of leprosy reactions, paraneoplastic syndrome, cutaneous lymphoma and dermatomyositis were made, and the histopathological findings were compatible with erythema multiforme. Prednisone was then prescribed at a dose of 20 mg/day for 10 days and then tapered. Due to almost none improvement of the skin lesions, worsening of muscle weakness, progressive dysphagia, arthritis of the hands and knees, and increased CPK levels (3.128 U/L), the patient was admitted at the hospital. In addition, the investigation of occult neoplasms was initiated, along with prescription of prednisone 1 mg/kg/day, being dermatomyositis the main diagnostic hypothesis. Contrasted computed tomography scan of the abdomen showed a suggestive image of gallbladder neoplasia with lymph node metastasis, confirming the diagnosis of neoplasm-related dermatomyositis. Directed treatment consisted of pulse therapy with methylprednisolone 1g given intravenously per day during 3 days, and subsequent cholecystectomy coupled with lymphadenectomy of hepatic and retroperitoneal wire. The histopathological findings showed an association of two well characterized populations of cells, that is, a

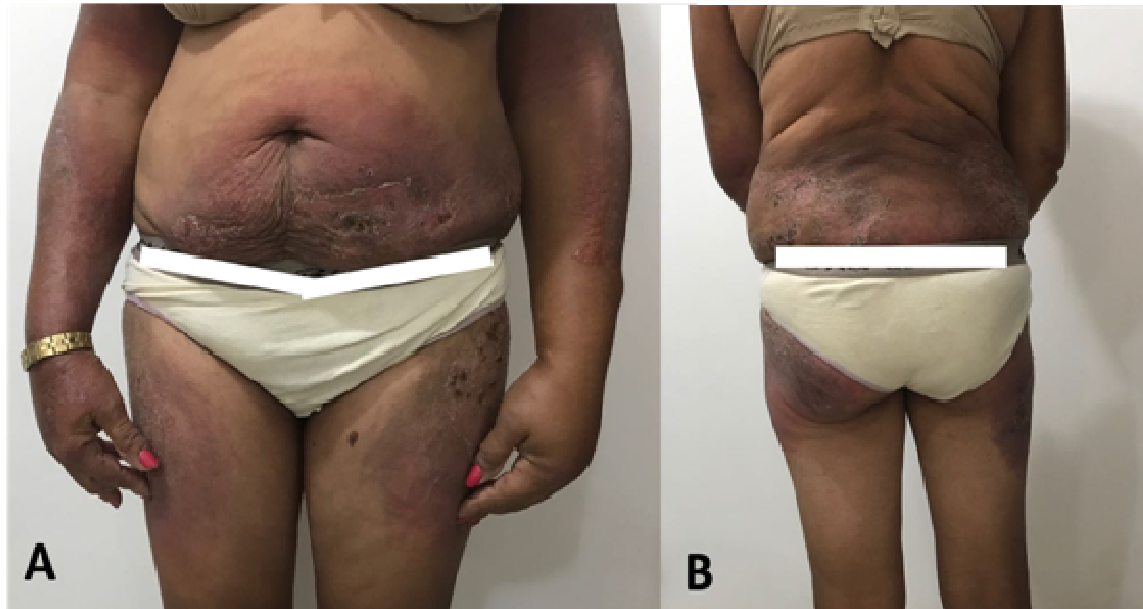


Figure 2. (A). Erythematous-violet scaly plaques in the periumbilical region and proximal third of the thighs (extensor face). (B). Erythematous-violet scaly plaques on flanks, proximal third of the thighs and buttocks (Holster sign).

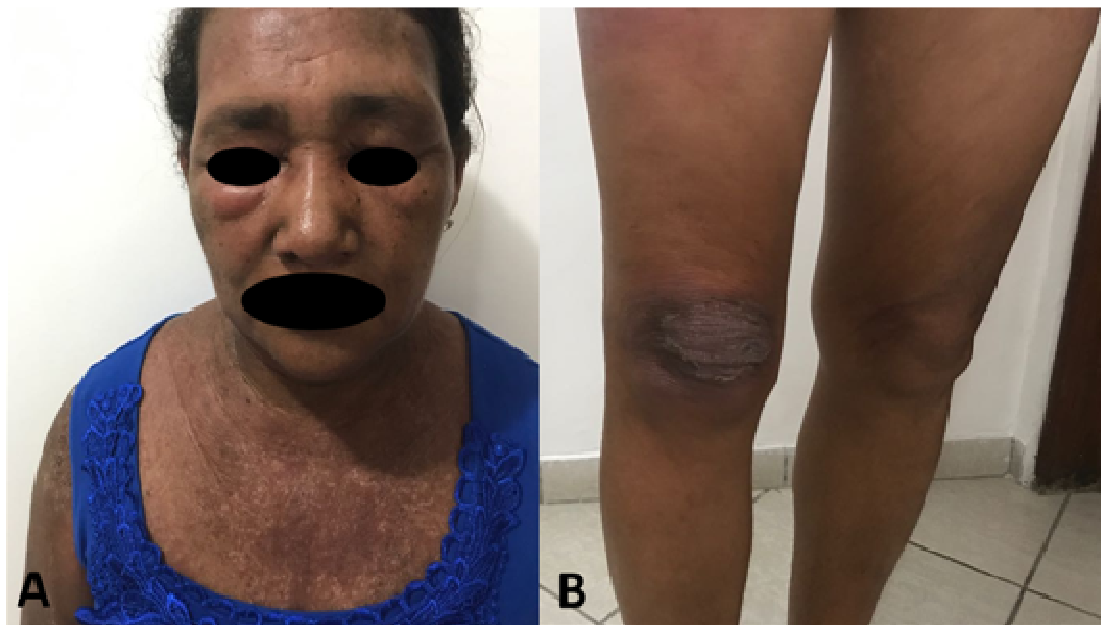


Figure 3. (A). Erythema and periorbicular edema, mainly at the right side (heliotrope). (B). Erythematous-violet scaly plaque on the right knee (Gotttron's sign).

moderately differentiated adenocarcinoma associated with a neuroendocrine carcinoma, compatible with primary mixed adenoneuroendocrine carcinoma (MANEC) of the gallbladder (Figure 4).

A few days after surgery, the patient was discharged from the hospital with improved muscle strength, expressive reduction in CPK levels (from 3.128 to 97 U/L)

and evident amelioration of cutaneous lesions. Follow-up included adjuvant chemotherapy with capecitabine. After almost 8 months of outpatient care, the neoplasm relapsed and, due to its advanced stage (multiple hepatic and pulmonary metastasis, unfavourable performance status), the patient was palliated and then died.

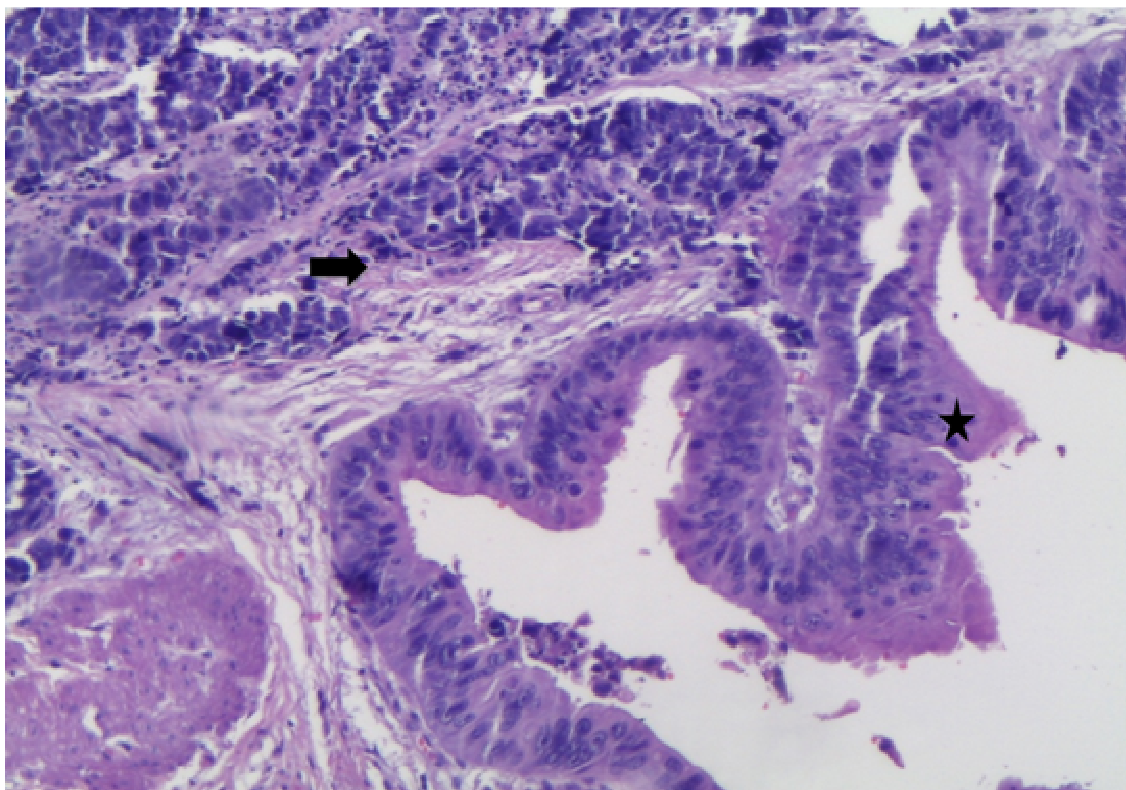


Figure 4. Histopathological image of mixed adenoneuroendocrine carcinoma (MANEC) of the gallbladder in the presented case, demonstrating both cell types: neuroendocrine carcinoma cells (upper part of the image, left sided; arrow), and adenocarcinoma cells (bottom part of the image, right sided; star). Hematoxylin & Eosin, 400 x.

DISCUSSION

The most common neoplasm of the gallbladder is the adenocarcinoma (Kamboj et al., 2015). More commonly observed in the gastrointestinal tract, pancreas and lungs (Song et al., 2012), neuroendocrine tumors may develop virtually at any body organ, with primary neuroendocrine neoplasm of the gallbladder being extremely rare (0.5% of all gallbladder tumors) (Mondolfi et al., 2011; Song et al., 2012; Kamboj et al., 2015). Though their relatively low incidence, the potential aggressiveness of these tumors was shown to be high (Song et al., 2012; Kamboj et al., 2015), which points to the need for early diagnosis (Kamboj et al., 2015). Composite tumors presenting with neuroendocrine and glandular cell types, in turn, are also of rare occurrence in the gastrointestinal tract, and when present, seem to display a preference for appendix, colon, duodenum, stomach and esophagus (Mondolfi et al., 2011).

When it comes to gallbladder tumors, many patients may not experiment signs and symptoms related to it until disease is advanced, so that surgical treatment may no longer be applicable at the time of tumor identification (Song et al., 2012). In such scenario, chemoradiation may be the only treatment option (Kamboj et al., 2015). In this regard, to the best of our knowledge, the case presented herein reports the first occurrence of the

association between MANEC of the gallbladder and paraneoplastic dermatomyositis. In fact, a recent search in Pubmed database (December, 2018) returned only six case reports of carcinoma of the gallbladder (either neuroendocrine or adenocarcinoma) associated with dermatomyositis, when using the terms “gallbladder” and “dermatomyositis”. Of note, none of them were described as a MANEC.

Reinforcing the pattern of aggressiveness of this type of neoplasm, even with free edges at the time of surgery in the present case reported, 8 months later the disease presented itself again with metastatic compromise, ending in death in less than 2 months after the beginning of jaundice.

It is a well-established recommendation that as soon as the diagnosis of dermatomyositis is made, the search for occult neoplasms becomes immediately mandatory, as such association may be present in a considerably high and variable amount of patients (12.1% in a recent meta-analysis (Qiang et al., 2016); 9-32% (Dalakas, 2015) and 10-15% (McGrath et al., 2018) in other studies). The risk of malignancy seems to be particularly high in the first 3 years after disease onset (Dalakas, 2015), at about 10-15% of the cases (McGrath et al., 2018).

Regarding the affected organs, paraneoplastic dermatomyositis is most commonly associated with ovarian cancer, breast cancer, melanoma, non-Hodgkin's

lymphoma and nasopharyngeal cancer (this one in Asians) (Dalakas, 2015). Other organs may also represent the primary tumor, such as lungs, esophagus, cervix and bladder (McGrath et al., 2018), as well as stomach, pancreas, colon, rectum, testis, prostate, penis and kidney. Furthermore, myeloma, Kaposi's sarcoma, meningioma and leukemia may also be observed (Junior et al., 2014).

The histogenesis of MANEC in the gallbladder remains to be determined, taking into account that no neuroendocrine cells are observed in normal gallbladder (Acosta et al., 2015). In an attempt to better clarify this issue, some hypotheses have accumulated in the past years, among which stem/progenitor cells were described as possible "starting points" for multiple cell type differentiation (Mondolfi et al., 2011). In line with this observation, intestinal metaplasia and transdifferentiation are also hypothetical mechanisms which could respond for MANEC onset (Meguro et al., 2014).

Histopathologically, MANEC is characterized by adenocarcinoma cells in the surface of the tumor (often with tubular or papillary pattern), with the neuroendocrine elements found as an invasion in the perineural and vascular areas (Harada et al., 2012; Meguro et al., 2014). Advances in immunostaining techniques allowed to more accurately classify different cell types, avoiding the misinterpretation of neuroendocrine cells usually taken as poorly differentiated adenocarcinoma cells (Acosta et al., 2015).

According to the World Health Organization classification, for a tumor to be classified as a MANEC, a pattern of at least 30% from each component (neuroendocrine and glandular) must be observed in the studied sample (Acosta et al., 2015). More importantly, the presence of the neuroendocrine component informs about worse prognosis, as the lymph node metastasis arise from neuroendocrine cells (Harada et al., 2012; Meguro et al., 2014).

Supporting the rarity of the case reported, in a study including 447 patients with gallbladder neoplasms, 416 were given the diagnosis of adenocarcinoma, 19 were identified as neuroendocrine carcinomas, and only one of them fulfilled criteria for MANEC classification (Kamboj et al., 2015). In face of this unusual occurrence, with few cases reported worldwide (Song et al., 2012), MANEC's real incidence remains to be determined (Acosta et al., 2015).

CONCLUSION

The case presented in this manuscript describes, for the first time, the occurrence of paraneoplastic dermatomyositis secondary to MANEC of the gallbladder. The aforementioned findings highlight the importance of effectively screening for gallbladder neoplasms when treating dermatomyositis, in face of the potential aggressiveness of this composite tumor. In sum, physicians must be aware of such possible association, once early diagnosis positively impacts in prognosis.

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